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VOL. I. No. 4 OCTOBER, 1939

BRITISH HEART JOURNAL

FOR THE STUDY OF
CARDIOLOGY AND THE CIRCULATION

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THE CARDIAC SOCIETY OF GREAT BRITAIN AND IRELAND

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

PUBLISHED QUARTERLY SUBSCRIPTION 25/- PER ANNUM

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THE EFFECT OF POTASSIUM ON THE HEART IN MAN

BY

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Received May 18, 1939

It is just one hundred years since Blake (1839) reported his " observations on the physiological effects of various agents introduced into the circulation." Among these were various salts of potassium, and he showed that when potassium carbonate, for instance, in doses of fifteen grains dissolved in six drachms of water was injected into the jugular vein in dogs, the animal was dead in forty-five seconds. He concluded that the action was a direct one upon the heart and that it was not harmful in therapeutic doses on account of the speed with which it was excreted by the kidneys.

During the intervening century it has been left to the physiologists to investigate the action of potassium salts upon the heart, work which has naturally been carried out upon the experimental animal. So far as the clinician was concerned, potassium, originally in the form of the citrate and the acetate and later as the chloride, rapidly came into favour as a diuretic, and, while there was a general feeling that in excess these salts might have their disadvantages, few, if any, experiments were carried out in man. Smillie in 1915 reported five cases of chronic nephritis to whom he had given 5 or 10 grammes of potassium chloride, and in one of these there was a sudden attack of intense cyanosis and prostration, preceded by præcordial pain, from which the patient took a fortnight to recover. From his work on potassium chloride as a diuretic, Blum (1920) recommended extreme caution in its use in patients with cardiovascular disease. Magnus-Levy (1920) also reported toxic effects from the use of potassium salts in a few patients with heart disease, and Webster (1927) stated that potassium salts by mouth " may cause irregularity of the heart and aggravation of symptoms of already existing renal or heart disease."

Methods of Present Investigation

As the result of the observation of certain changes in the electrocardiograms from patients that were receiving potassium salts, it was decided to carry out a more careful study of the effects of such salts upon the heart in man, not only to gain some information as to possible dangers in their therapeutic applica-

tion, but also in an attempt to throw some light on their function in the ætiology of certain disorders of the heart.

The effect of potassium salts upon the heart has been studied in 24 patients, including the 5 already reported upon elsewhere (Thomson 1939) ; in addition the serum potassium and its alterations under certain conditions have been studied in a further 11 patients with heart disease. For the purpose of this paper, however, only the first 24 will be considered. This group included twelve patients with hypertension, two of whom had diabetes mellitus and one slight thyrotoxicosis ; five with advanced chronic nephritis ; two with mitral stenosis and normal rhythm ; one with coarctation of the aorta ; one with luetic aortic incompetence ; one with thyrotoxicosis ; one with the " menopausal syndrome " ; and one with allergy.

Potassium was given by mouth in the form of the citrate and the chloride, the usual dosage in the case of both salts being 5 grammes thrice daily at 8.30 a.m., 1.30 p.m., and 7 p.m., but several patients were given smaller amounts. Blood for the estimation of the serum cations was taken at noon, the patient having had nothing to eat since breakfast at eight ; it was obtained from the antecubital vein without the use of stasis and the serum was separated one and a half hours later.

Electrocardiograms were practically all taken at the same time of day—shortly before the midday meal—with the patient in bed, and every care was taken to ensure that the standardization was uniform, i.e. 3 millivolts=3 cm. displacement of the fibre. In all instances they were taken both before and during the administration of potassium, and generally at least one was taken a week after it had been stopped.

The serum cations were estimated by the following methods ; potassium, Kramer and Tisdall (1921) as modified by Peters and Van Slyke (1932) ; sodium, Butler and Tuthill (1931) ; calcium, Kramer and Tisdall (1921) as modified by Clark and Collip (1925). The urease method was used for the estimation of the blood urea, and the hæmoglobin was estimated by means of the Haldane hæmoglobinometer, the blood always being taken from the ear without stasis at the same time of day.

Results : (A) Potassium and the T Wave

Potassium salts were administered to 24 patients ; changes in the T wave were observed in 15, but they were either absent or insignificant in 9. The 15 that showed such changes were 5 with hypertension, 5 with chronic nephritis, and 5 others ; details are given in Table I.

The change in the T wave consisted of an increase in the height of the wave in 14 cases. This increase in height occurred in different leads, in one lead only or in all three, and in practically every case disappeared after potassium was stopped. Fig. 1 shows a typical example of the change obtained. In the fifteenth case the changes in the T wave were quite different in type, as can be seen from Fig. 2 (see page 273).

TABLE I

INCREASE OF THE HEIGHT OF THE T WAVE IN THE ELECTROCARDIOGRAM WITH INCREASE IN THE SERUM POTASSIUM

Case Number	Diagnosis	Serum Potassium in mg. per 100 c.c.		Electrocardiographic Changes in the Height of the T Waves
		Before Administration of Potassium	During Administration of Potassium	
7	Malignant Hypertension	11·9	18·9	Increase
3	Malignant Hypertension	10·1	22·9	Increase
1	Essential Hypertension	17·2	21·8	Increase
8	Essential Hypertension	19·6	21·5	Increase
2	Essential Hypertension	15·5	21·2	Increase
4	Chronic Nephritis ..	20·5	31·6	Increase
5	Chronic Nephritis ..	17·0	32·8	Increase
9	Chronic Nephritis ..	22·1	25·1	Increase
10	Chronic Nephritis ..	20·7	33·1	Increase
22	Chronic Nephritis ..	22·6	—	Increase
11	Mitral Stenosis	19·1	28·9	Increase
12	Aortic Incompetence ..	17·8	31·8	Increase
6	Thyrotoxicosis	16·1	23·0	Increase
23	Menopausal Syndrome..	16·4	—	Increase
13	Allergy	19·4	21·7	Increase
14	Malignant Hypertension	15·1	22·2	No Increase
24	Essential Hypertension..	15·3	—	No Increase
15	Essential Hypertension ; Diabetes Mellitus ..	19·7	21·6	No Increase
16	Essential Hypertension ; Diabetes Mellitus ..	15·1	18·1	No Increase
17	Essential Hypertension ; Thyrotoxicosis.. ..	19·1	25·3	No Increase
18	Essential Hypertension..	18·8	20·4	No Increase
19	Essential Hypertension..	17·0	16·7	No Increase
20	Coarctation of Aorta ..	16·2	17·3	No Increase
21	Mitral Stenosis	15·6	15·7	No Increase

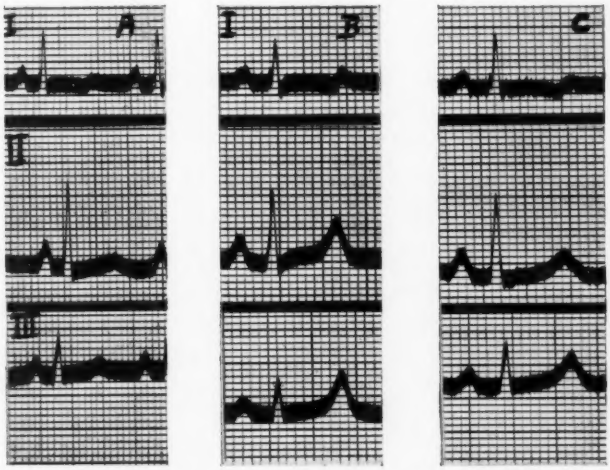

FIG. 1.—Electrocardiograms from case 4, with chronic nephritis.

(A) Before administration of potassium salts.

(B) After 71 g. of potassium chloride given during 7 days, showing heightened T waves in all leads (serum potassium increased from 20·5 to 31·6 mg. per 100 c.c.).

(C) After 14 days without any potassium salts, showing T waves diminished in height (serum potassium 21·4 mg. per 100 c.c.).

In Table II the findings in six of these patients have been given in more detail. The increase in the height of T varied considerably, from 1 to 4 mm., and in some cases it was more than doubled in height. This alteration in the height of the T wave could not be correlated with any change in the rate of the heart, in the height or width of QRS, or in the length of the S-T segment.

TABLE II

MORE DETAILED EFFECTS OF THE ADMINISTRATION OF POTASSIUM IN SIX CASES

Number of Days from Start	Serum Potassium	Serum Sodium	Serum Calcium	Blood Urea	Haemoglobin per cent.	Height of T Wave in EC. in mm.			Dosage of Potassium Salts
	in mg. per 100 c.c.					T_I	T_{II}	T_{III}	
					Case 1. *Essential Hypertension*				
0	17·2	323	10·2	31	102	2·0	2·0	−0·5	Days 0–14, pot.
7	18·3	324	9·5	26	112	2·0	2·0	−0·5	cit. 15 g. daily.
14	21·3	313	10·0	26	110	3·0	3·0	−1·0	Days 7–14, pot.
21	21·8	325	10·7	24	88	4·5	2·0	−1·5	chlor. 15g. daily.
28	16·5	324	10·5	24	102	2·0	1·5	−0·5	
					Case 2. *Essential Hypertension*				
0	15·5	328	11·4	23	110	3·0	2·5	−0·5	Days 0–14, pot.
7	18·5	325	—	28	112	6·5	3·5	−2·0	cit. 15 g. daily.
14	21·2	333	11·0	27	108	5·0	4·5	−0·5	Days 7–14, pot.
21	15·3	326	10·7	21	102	2·0	2·0	−0·5	chlor. 15 g. daily.
					Case 3. *Malignant Hypertension*				
0	10·1	310	10·3	16	86	−0·5	D*	2·0	Days 0–12, pot.
7	11·8	311	10·5	22	82	0·0	D	1·5	cit. 15 g. daily.
12	22·9	306	11·2	33	98	1·5	4·0	2·5	Days 7–12, pot.
24	7·5	307	10·3	20	84	−2·0	D	1·5	chlor. 15 g. daily.
					Case 4. *Chronic Nephritis*				
0	—	—	—	—	—	D	1·0	1·0	Days 5–12, pot.
2	20·5	—	9·3	143	65	—	—	—	cit. 71 g.
12	31·6	—	11·0	148	56	D	5·0	5·0	—
26	21·3	—	9·6	180	55	D	3·0	3·5	
					Case 5. *Chronic Nephritis*				
0	17·0	—	9·6	62	96	−2·0	−1·5	0·5	Days 1–8, pot. cit. 15 g. daily.
8	32·8	—	9·9	70	92	1·0	2·0	1·5	Days 6–8, pot.
15	16·0	—	9·6	81	82	1·0	−0·5	−1·5	chlor. 15 g. daily.
					Case 6. *Thyrotoxicosis*				
0	16·1	—	10·8	30	92	1·0	1·5	1·0	Days 0–6, pot. cit. 145 g.
11	23·0	—	10·8	44	102	2·0	4·0	1·0	Days 7–11, pot.
21	19·4	—	9·9	26	105	1·5	2·0	1·5	cit. 15g. daily, pot. chlor. 15g. daily.

* D=Diphasic.

The amount of potassium salts ingested before this change was produced varied considerably. In one patient it occurred after only 20 g. of the citrate given during four days. In others, 210 g. of the citrate and 105 g. of the chloride given over a period of two weeks did not produce it. Of the 15 patients who showed changes in the T wave, 7 received the citrate alone, 7 received both citrate and chloride simultaneously and 1 received only the chloride, while of the 9 who showed no such change, 7 received the citrate alone and 2 received both salts.

The concentration of serum potassium at which this change occurred was most inconstant, a more constant figure being the increase in its level. As can be seen from Table I, in thirteen of the patients who showed a change in the T wave, and in whom figures are available for the serum potassium both before and during the administration of potassium salts, the rise in the serum potassium varied from 1·9 to 15·8 mg. per 100 c.c., the average being 8·3 mg., while the comparable figures for the patients with no change in the T wave were −0·3 to 7·1 mg. per 100 c.c., giving an average of 2·6 mg. In only one instance did the serum potassium fail to return to practically the original level, and in this case the T wave also failed to return to its original height.

This heightening of the T wave was accompanied by a slight or moderate elevation of the S-T segment in a few of the patients (Fig. 1), and inversion occurred in one case (Fig. 2).

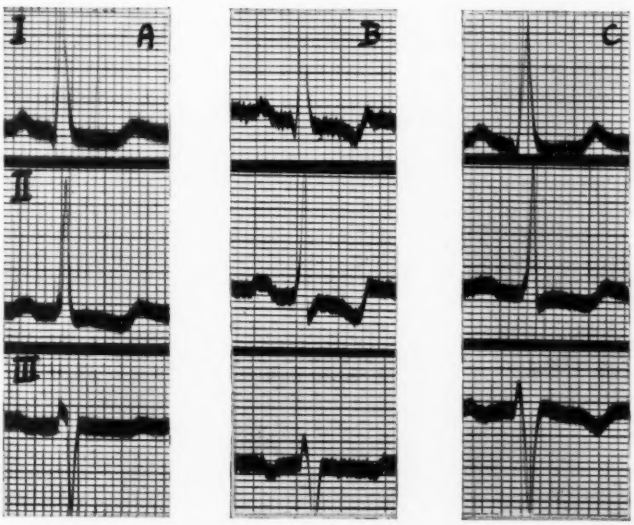

FIG. 2.—Electrocardiograms from Case 12, with luetic aortic incompetence.

(A) Before administration of potassium salts.
(B) After 192 g. of potassium citrate given during 14 days, showing T waves increasingly diphasic in all leads (serum potassium increased from 17·8 to 31·8 mg. per 100 c.c.).
(C) After 7 days without any potassium salts, when the T waves were almost, and the serum potassium was quite, back to the original levels.

No constant change was found in any instance in the levels of the serum sodium or calcium or the blood urea.

(B) Potassium and Conduction

In two patients the administration of potassium salts was accompanied by impairment of conduction, and, in view of the importance of these observations, it is proposed to describe them in detail.

Case 23. A woman, aged 45, gave a three years' history of short attacks of palpitation, which began and ended gradually. She had lost weight, and had some symptoms suggestive of thyrotoxicosis, but on examination no evidence of this could be found and the basal metabolic rate was only +12 per cent. The blood pressure was 145/90 mm., the pulse was 96, and regular, the heart was not enlarged, and the heart sounds were pure and clear. A diagnosis of the menopausal syndrome was made. Serum potassium was 16·4 mg.; serum calcium, 11·9 mg. ; blood urea 20 mg., in each case, per 100 c.c.

Potassium chloride was given in doses of 5 g. thrice daily, combined after one day with the same amount of potassium citrate. During the second night

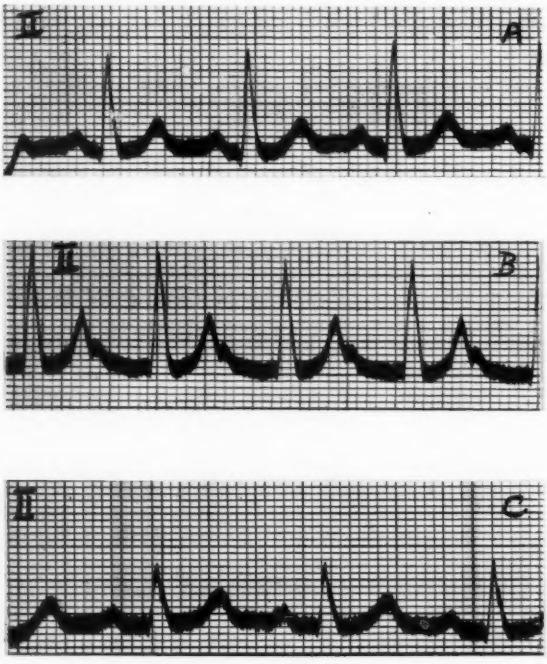

Fig. 3.—Electrocardiograms in Case 23.

(A) Showing the P-R interval within normal limits.

(B) Three days later, after the patient had received 40 g. of potassium chloride and 15 g. of potassium citrate, showing lengthening of P-R interval and heightened T wave.

(C) Seven days from the start, when no potassium salts had been given for three days, showing the P-R interval again within normal limits and the T wave back to its original height.

of potassium administration, after she had received 35 g. of the chloride and 10 g. of the citrate, she complained of a heavy feeling in the legs, and the pulse was found to be 120 per minute and regular. Next day, three hours after another 5 g. each of the chloride and the citrate, there was prolongation of the P-R interval and heightening of the T wave (Fig. 3 B). Potassium salts were stopped on the fourth day, when the patient felt very hot and flushed and complained of a sinking feeling, nausea, and a tingling sensation in the arms, but not of palpitation.

Three days later the P-R interval had become normal (Fig. 3 C) and remained so in a subsequent record.

Case 11. A woman, aged 46, was admitted on account of increasing dyspnœa on exertion and cough ; during the last three months orthopnœa and swelling of the ankles had developed.

On examination she was found to be a typical case of mitral stenosis with normal rhythm and signs of early congestive heart failure.

The serum potassium was 20·6 mg. ; serum calcium, 10·1 mg. ; and the blood urea 39 mg., in each case, per 100 c.c. Hæmoglobin, 100 per cent.

After a week in hospital, the administration of potassium chloride was started in doses of 5 g. thrice daily. Two hours after the fourth dose she felt cold and sick and complained of a sensation of tingling everywhere and of sinking through the bed ; the pulse was 112 per minute and regular. An hour later, while still regular, it had fallen to 40, rising two hours later to 60 per minute and still regular. On the following day, that is after the patient had taken 30 g. of potassium chloride in all, it was stopped on account of vomiting and evacuation of the bowels, the pulse being 42 per minute and regular.

Eight days later, the serum potassium being 19 mg. per 100 c.c., administration of potassium salts was begun again, and during the next sixteen days 125 g. of potassium citrate was given without the production of any toxic effects. On the seventeenth day potassium chloride, in doses of 3 g. thrice daily, was combined with the citrate which was now being given in doses of 5 g. thrice daily, and the following day, twenty-five minutes after her second dose of each of these salts, she complained of feeling queer and the pulse was found to be 72 per minute and regular. Fifty minutes later it was 30 and regular, the patient complaining of no discomfort ; and after another thirty minutes the pulse was 44, while an hour later it was 56 per minute and regular.

In view of these signs of toxicity, it was decided to follow the course of their development more carefully by giving the patient a dose of the two salts and following the effect on the heart by means of the electrocardiograph and by recording the rate of the heart at the apex every minute. Accordingly, the next day, after a control electrocardiogram showing normal sinus rhythm (Fig. 4 A), a sample of blood was obtained which gave the following results, serum potassium, 19·1 mg. ; serum calcium, 11·6 mg. ; blood urea, 30 mg., in each case, per 100 c.c. The patient was then given 5 g. of potassium chloride and 5 g. of potassium citrate by mouth. Thirty minutes later there was some increase in the height of the T wave. Forty-three minutes after the ingestion of the potassium salts, the ventricular rate suddenly slowed and became irregular,

and there were two periods of cardiac asystole and slight prolongation of the P-R interval (Fig. 4 B). (It should be noted that T III was negative in the control). Venu-puncture was performed as soon as this electrocardiogram was taken and the serum potassium was 28·9 mg. ; serum calcium, 11·5 mg. ; and the blood urea, 34 mg., in each case, per 100 c.c.; the patient complained of feeling faint, but objectively the only change noted was deepening of the respirations and some pallor of the face.

FIG. 4.—Electrocardiograms in Case 11.

(A) Prior to administration of potassium, showing normal sinus rhythm.

(B) 43 minutes after administration of 5g. of potassium chloride and 5g. of potassium citrate, showing period of cardiac asystole.

(C) 71 minutes after administration of potassium, showing bradycardia with varying sites of impulse formation.

On account of the persistent bradycardia and irregularity, atropine sulphate gr. 1/50 was given subcutaneously eight minutes later, that is fifty-one minutes after the ingestion of the potassium salts, and an electrocardiogram two minutes later showed similar changes to the previous one. Others were taken subsequently, one of which, seventy-one minutes after the ingestion of the potassium salts, is reproduced in Fig. 4 C and shows a shifting pacemaker, situated sometimes in the A-V node, sometimes in the S-A node. In lead I of this electrocardiogram, which is not reproduced, ventricular complexes occur without any associated P waves. When observations were discontinued, 107 minutes after

the ingestion of the potassium salts, the ventricular rate was 72 per minute and regular. An electrocardiogram taken nearly four hours after the beginning of the experiment revealed normal sinus rhythm with the T waves still heightened; six days later another was essentially similar to the control record, and analysis of the blood showed that it was practically the same as before the administration of potassium, i.e. serum potassium 17·0 mg., serum calcum 10·5 mg. and blood urea 42 mg., in each case per 100 c.c.

In this patient potassium salts produced changes in intracardiac conduction, just over forty minutes after their ingestion, changes which the electrocardiogram showed, consisted principally of suppression of the sinus as the inaugurator of the cardiac impulse, this function being finally taken over by either the A-V node or bundle. Two points of interest are that conduction in the ventricles was not affected, and that when the sinus again took over its normal function as pacemaker there was no evidence of more than a very slight delay in conduction between the auricles and ventricles.

(C) Other Signs of Toxicity

Apart from the effects on the heart just described, few definite signs of toxicity were observed from giving potassium salts. All the patients disliked the taste of the chloride mixture, a taste which it is wellnigh impossible to disguise. Vomiting occurred in five patients, but generally in those with malignant hypertension or chronic nephritis, in whom the least disturbance was liable to produce vomiting, and in only one of these was it persistent. Only one patient complained of symptoms that might be cardiac, namely thumping of the heart. Three, including the two described in the preceding section, complained of tingling in the arms and legs followed by a sensation as if the limbs were dead or heavy ; and sweating occurred in one. Diarrhœa was not encountered in any of the patients.

Discussion : (A) Potassium and the T Wave

During the last sixty years the effect of the inorganic cations, including potassium, upon the heart has been very fully studied by the physiologists, notably Ringer (1880–82), Howell (1899, 1902, 1905–06), Greene (1899), Hald (1905), and Hering (1915). All these, however, have made use of the experimental animal, including the frog, rabbit, cat, and dog, and little work has been done upon the effects of these cations on the human heart, the inference having been accepted that comparable effects might be expected in the case of man.

One of the few investigations carried out in man is that of Harris and Levin (1937), who injected various amounts of a 5 per cent. solution of potassium chloride into six normal subjects and reported that the height of T was sometimes increased, but that " no definite correlation could be found between the magnitude of the changes in the electrocardiogram and the concentration of potassium in the blood stream." The two most direct studies with the experimental animal have been those of McLean and his colleagues (1933) and of Winkler and his colleagues (1938). The former, working with the perfused rabbit's heart, showed that increasing the potassium content of the perfusing fluid resulted in a high T wave, and diminution in a low or negative T wave.

Winkler, Hoff, and Smith (1938) injected isotonic solutions of potassium chloride intravenously into dogs and found that the first change to occur was an increase in the height of the T wave, which progressed until T equalled the QRS complex in amplitude. Wiggers (1930) also has shown that the intravenous injection of potassium chloride in the dog is followed by a pronounced increase in the height of T.

It is not proposed here to discuss all the factors that are known to cause an increase in the height of the T wave, but some of them appear to have a bearing on the present problem, and among these one of the most important is the effect of asphyxia on the heart. As has been shown by D'Silva (1934) and Cattel and Civin (1938) in the case of the cat, and by Dennis and Mullin (1938) in the case of the dog, asphyxia results in an increase in the concentration of the serum or plasma potassium. Most workers are agreed that asphyxia results in an increase in the height of the T wave. Thus Greene and Gilbert (1922), producing anoxæmia in dogs by a rebreathing method, found that as the anoxæmia developed the most typical change in the electrocardiogram was that T became increasingly taller till it was as high as the original R wave, and that this change "apparently did not depend on a change in the position of the heart." Similar results were obtained in dogs by Haggard (1921), and Kountz and Hammouda (1932), working with a heart-lung preparation in the same animal, found that excess of carbon dioxide increased the height of T in all leads.

Similar changes in the T wave have been obtained in alkalosis and acidosis. Barker, Shrader, and Ronzoni (1939) found in man that alkalosis resulted in a lowering of the T wave, the opposite effect being produced by acidosis. In dogs Schott (1926) reported that the intravenous injection of hydrochloric acid was followed by a rise, and of sodium bicarbonate by a fall in the height of the T wave. Carter, Andrus, and Dieuaide (1924) found that upright T waves in the cardiogram of a dog being perfused with a solution of pH 7·1 became negative when the reaction of the perfusate was made less acid (pH 7·4.) Allott and McArdle (1938) report that in a severe case of tetany and alkalosis due to vomiting from pyloric obstruction the serum potassium was as low as 7·6 mg. per 100 c.c., which is of interest in this connection.

Pitressin has also been shown to cause an increase in the height of the T wave in dogs (Resnik and Geiling (1924–25), Gruber and Kountz (1930), and Melville (1938)), and this and the other effects on the heart have been attributed by these authors to anoxæmia of the heart. D'Silva (1934) found that pitressin caused a rise in the serum potassium.

In view of these findings, namely that an increase in the height of the T wave is caused by asphyxia, acidosis, pitressin, and potassium, taken in conjunction with the correlated changes in the level of the serum potassium, there would seem to be some justification for the hypothesis that the common factor—potassium—may be the cause of these changes. Andrus and Carter (1924) in their work on the effect of changes in pH upon the heart suggested that these changes might be elicited by a disturbance of ionic equilibrium between the cell contents and the tissue fluid, and, in view of the fact that potassium is dominantly an intracellular ion, it is only to be expected that any such dis-

turbance of ionic equilibrium might be accompanied by an increase of potassium in the extracellular fluids, including the bloodstream. Whether potassium acts directly or indirectly, and the mechanism of its action are questions which can be discussed more conveniently in association with the changes produced in intracardiac conduction.

(B) Potassium and Conduction

As the two cases just described show, the effects of potassium on the heart in man are comparable with those in the experimental animal, the main difference being that in man there is much less effect on the ventricle. This is probably due to the fact that much larger amounts are needed to affect the ventricle in man than it would be possible to give with safety.

The problem which is of outstanding interest here is the mechanism whereby potassium produces these effects. Is the block due to a direct effect of potassium upon the myocardium, or is it an indirect effect mediated through the vagus ? That there is a close association between the effects of the vagus and of potassium on the heart has been suggested by many workers since the original work of Howell (1905–06) who showed in frogs and terrapins that an increase of potassium in the circulating medium enhanced the sensitiveness of the heart to vagus inhibition, and interpreted these results as meaning that the vagus impulses act indirectly by increasing the amount of diffusible potassium compounds in the heart tissue. Subsequently (Howell and Duke, 1908) he found that in the isolated mammalian heart stimulation of the vagus caused an increase in the potassium content of the circulating medium. Among more recent workers who have confirmed these findings may be quoted Herz (1935) who found that potassium ions have a marked effect upon the sensitivity of the heart of the frog to vagal stimulation, and Lenhartz (1936) who found in the isolated auricle of the tortoise an increase in the potassium content of the perfusion fluid following stimulation of the vagus.

A similar close association has been shown to exist between acetylcholine and potassium. Thus in the heart of the frog, Chang and Gaddum (1933) found that potassium produced effects similar to those given by acetylcholine. In the cat, Brown and Feldberg (1936) found that potassium increased the response of the superior cervical ganglion to preganglionic stimuli and liberated acetylcholine from the ganglion, while Feldberg and Guimarāis (1936), finding that intra-arterial injections of potassium chloride liberated acetylcholine from various organs, consider this supports the suggestion that discharge of acetylcholine may be effected by potassium ions mobilized in the passage of the nerve impulse. Fischer (1936) has suggested that different vagal fibres affecting the heart are not only functionally different, but that there exist several chemical transmitters for the vagal action, one of which is potassium and another acetylcholine.

Further light is thrown on the problem by the careful study of Greene and Gilbert (1922) of the effects of anoxæmia on the heart. Working with the dog and producing a gradually increasing anoxæmia, they found that this inhibited sino-auricular rhythm or drove the rhythm to a lower focus in the

tail of the sino-auricular node. When sino-auricular rhythm was inhibited, an auriculo-ventricular rhythm became dominant, but at a slower rate. If at this stage the anoxæmia was relieved, normal rhythm was restored, but, if the anoxæmia was allowed to develop, the rhythmic centre was driven down into the left bundle branch. Section of both vagi invariably abolished these early changes and was followed by the onset of sinus tachycardia. They therefore concluded that the early anoxæmic changes were a vagal effect, and that it was only when an extreme degree of anoxæmia was produced that suppression of rhythm was obtained due to cardiac anoxæmia. Their criticism of other workers, such as Mathison (1910–11), who considered that the heart block of asphyxia was not due to a vagal effect, was that these workers had used such rapid methods of inducing anoxæmia that they missed the early stage of slowing due to the vagus and only obtained the late stage of direct cardiac anoxæmia. The interest of these findings of Greene and Gilbert is that the changes they produced in the heart were very similar to those obtained in our second case. In both instances there was suppression of the sino-auricular node as pacemaker, the auriculo-ventricular node taking on this function, and in both the first change was a heightening of the T wave. It was on these grounds that atropine was administered at the height of the block in our case, but in view of our ignorance as to how long the potassium effect persists it is not possible to decide whether the return of normal sinus rhythm was due to the atropine or not.

In other words we find that vagal stimulation and acetylcholine and potassium all produce the same effects on the heart, and that the two former increase the extracellular concentration of potassium. Further Lenhartz (1936) has shown in the isolated auricles of the heart of the tortoise that when enough atropine is present to suppress the inhibitory action of vagal stimulation and of acetylcholine, neither of these last procedures produced any change in the concentration of potassium ions. There would therefore seem to be justification for advancing the hypothesis that these particular changes in the function of the heart are mediated through the action of the potassium ion. The exact mechanism of this action still awaits further elucidation.

Clinical Applications

While the pathological aspects of the relationship of potassium to cardiac pathology raise many interesting problems, with which it is not intended to deal here, there is a clinical aspect, now being investigated, which would seem to be worthy of attention.

Potassium salts, particularly in the form of the citrate, have long enjoyed a reputation as diuretics both in renal and cardiac œdema. The dose of potassium citrate, according to the British Pharmacopœia, is 10–60 grains (0·65–4 g.). Potassium chloride is included in the British Pharmaceutical Codex, where the dose of this salt is given as 15–60 grains (1–4 g.). As a rule, however, much larger doses are prescribed. Thus Blum (1920) gave 25 g. of the chloride daily in cases of chronic nephritis, while Osman (1927) gave his patients with Bright's disease 24 g. of potassium salts (12 g. of citrate and 12 g. of bicarbonate) daily. Keith and Binger (1935) recommended a standard daily dose equivalent to

5 g. of potassium (10 g. of chloride or 14 g. of citrate), and even larger amounts were given by Hawes and Vardy (1935) in nephrosis, a mixture containing 2 g. of potassium bicarbonate and 2 g. of citrate, every hour for long periods.

The general assumption has been that large doses of potassium salts by mouth are not toxic on account of the rapidity with which they are excreted in the urine. To quote the British Pharmaceutical Codex (1934), " Potassium chloride does not exhibit the depressant action of the potassium ion on the tissues, because it is excreted with such extreme rapidity that the blood never contains it in sufficient concentration to produce the specific effect." That this is not always the case, however, is shown by the figures in our cases, and particularly is this so in chronic nephritis, the very group in which potassium salts are usually administered as diuretics. In view of the marked disturbances which can be produced by the ingestion of potassium salts by mouth, their administration in patients with cardiovascular disease would seem to be contra-indicated, or at least they should only be given in small doses. A consideration of the treatment of the large number of elderly patients with enlargement of the prostate, who are given mixtures containing anything from 4 g. (60 grains) of potassium citrate three or four times a day both before and after operation, raises the interesting question as to the effect of such medication on a heart that is often far from healthy. Is this the solution of the problem as to why some of these patients occasionally die suddenly ?

A further clinical application is suggested by Camp's (1939) work on the potentiation of digitalis action by potassium. This investigator found in dogs that the administration of three or four doses of digitalis given every five minutes was without effect on the pulse or amplitude. If potassium chloride was given at this stage, however, marked slowing of the pulse occurred accompanied by an increase of amplitude. He suggests that digitalis exerts an early unrecognizable action on the heart which can be made manifest by potassium.

Summary.

1. Potassium salts, in the form of the chloride and the citrate in doses varying from 3–30 g. daily, have been given to twenty-four patients with various diseases, and the effect on the electrocardiogram has been observed.

2. In fourteen of these the administration of potassium salts was followed by an increase in the height of the T wave in one or more leads. No correlation was found between the increase in the height of the T wave on the one hand and the amount of potassium given or the increase in the concentration of the serum potassium on the other, except that in the fourteen patients who showed this change the average increase in the level of the serum potassium was 8·3 mg. per 100 c.c., compared with 2·6 mg. per 100 c.c. in the patients who showed no such change.

3. In one patient the T wave, which was diphasic in all leads before the administration of potassium salts, became more deeply diphasic while they were being given.

4. In two patients definite degrees of heart block were produced by the administration of potassium salts. In one, there was prolongation of the P-R

interval, while in the other sino-auricular block and nodal rhythm resulted with marked slowing and irregularity of the heart rate.

5. The similarity of these changes to those produced by vagal stimulation, by acetylcholine, and by pitressin is discussed, and the hypothesis is advanced that in each case they may be mediated through the action of the potassium ion on the myocardium.

6. Certain clinical applications of this work are also discussed, and it is recommended that potassium salts should be used with the utmost caution in patients with cardiovascular or renal disease.

I am indebted to Professor O. L. V. S. de Wesselow for permission to carry out these investigations on patients under his care and for the interest which he has taken throughout this work.

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THE ÆTIOLOGY OF LUNG INFARCTION

BY

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Received June 8, 1939

The purpose of this communication is to try to show that the common hæmorrhagic infarct of the lung is usually an embolic rather than an autochthonous phenomenon. This is by no means a new idea; as will be evident enough from Ceelen's (1931) exhaustive review of the subject. But the alternative view, which supposes the pulmonary arteries to be a common site of autochthonous thrombosis, is still widely prevalent.

This report is concerned with a series of 1990 consecutive autopsies in which special attention has been given to dissection of the pulmonary arteries. These autopsies, as a series, may be regarded as fairly representative of general hospital cases. More than half of them were performed in the Department of Pathology at the University of Toronto from 1931 to 1936, and the rest at this School from 1937 to 1939.

There were in this series 155 cases presenting gross hæmorrhagic infarction of the lung. This was exclusive of septic infarction, for here we were concerned only with the bland, non-infective type of lesion. According to our interpretation of the autopsy findings no less than 136 of these were due to embolism, 10 only were due to thrombosis, and in 9 no definite arterial occlusion was found.

Identification of Emboli

It is not always easy to distinguish between thrombus and embolus, but there are criteria that make it possible in most instances. The identification of an embolus may rest upon some of the following features : it may be loose-lying, coiled, jumbled, twisted, impacted (Fig. 1), or riding a bifurcation ; it may have a branching conformity that does not correspond with that of the vessel in which it lies, or it may have freshly broken ends. More important perhaps than its shape and location is the quality of the clot. The type of embolus with which we are concerned is usually a red clot composed chiefly of fibrin and red blood cells. Because it takes origin in slowly moving or stagnant venous streams, it is not unlike the clot that freshly drawn blood will form on standing in a test tube. On the other hand, thrombus that takes origin in the pul-

monary arteries is usually white or light pink, and composed chiefly of platelets and white cells, because it is laid down in a faster moving stream. It is always attached more or less securely to the vessel wall. It usually has a sessile base with gently shelving margins, and it is moulded to the shape of the vessel in

FIG. 1.—Embolus in a tertiary branch of the pulmonary artery. It looked like an autochthonous thrombus until it was hemisected, as seen here, when its jumbled and distorted laminations became apparent and also the fact that it was lodged at the mouth of a smaller branch. (Museum specimen, 24.25.1, B.P.M.S.)

which it lies. If one can find in the peripheral veins a potential source for the embolism, the problem is often facilitated ; for the embolus will then resemble the parent clot.

Difficulty may be encountered when both embolus and thrombus are present together, but this only happens in a minority of cases. More than half of the emboli in this series occurred alone, about one-third were accompanied by small amounts of autochthonous thrombus, and only a few, perhaps less than five per cent., were sufficiently obscured by superadded thrombus to render their identification difficult. In such doubtful cases we have usually put it down as thrombosis.

In order to make the distinction between thrombus and embolus it is obvious that one must have a satisfactory exposure of the whole clot. To accomplish this requires a technique of dissection that will permit of opening the second, third, and even fourth divisions of the pulmonary arteries without

too much mutilation of the lungs. We have found it relatively easy to adopt such a technique (Belt, 1936) as a routine procedure.

Hæmorrhagic Infarction of the Lung

The following table indicates the nature of the 155 cases in which infarcts were found.

TABLE I

Analysis of Hæmorrhagic Infarction of Lung

Certifiable Cause of Death	Cause of Infarction			
	Embolism	Thrombosis	Unknown	Total
Heart disease	70	3	1	74
Pulmonary embolism	22	—	—	22
Malignant neoplasm	17	2	2	21
Pulmonary tuberculosis	8	1	—	9
Cerebral softening	8	1	2	11
Various	11	3	4	18
Total number of cases	136	10	9	155

Cases with Embolic Infarcts

Pulmonary embolism was regarded as the main cause of death for purposes of certification in 22 cases, and as a contributory cause in 77; the remaining 37 of the 136 cases were examples of minor embolism, some of them showing only a single infarct.

Of all the pulmonary emboli encountered in this series of 1990 autopsies, not more than half were associated with infarction ; that is to say, there were about twice as many cases of embolism as of infarction. Since Virchow's time it has been well known that occlusion of a pulmonary artery is in itself insufficient to produce an infarct. There must be added factors, and it cannot be said that we know precisely what these are; nor does it lie within the scope of this paper to define them. Certain it is, however, that heart disease outshadows all other conditions as a concomitant of lung infarction. The theoretical explanation is that any lesion retarding the normal flow of blood through the left auricle produces increased pressure in the pulmonary veins, and this may lead to complete stasis and necrosis (hæmorrhagic infarct) in the event of an arterial occlusion.

In this series of 1990 autopsies there were 235 deaths registerable as from heart disease. The majority of them had congestive failure. Almost a third (70 cases) died with embolic infarcts of the lungs. Table II gives a survey of these.

There were 27 cases of rheumatic disease, 24 with mitral stenosis; with an average age of 39 years. An equal number had coronary disease, 21 with

coronary occlusion (old or recent) and 16 with angina pectoris ; their average age was 63 years. The remaining 16 were miscellaneous cardiopathies, with an average age of 54 years.

The second largest group in Table I consists of 22 cases of sudden death from pulmonary embolism. Twelve were recovering from operations (9 laparotomies and 3 prostatectomies), 7 from fractures (5 of the femur, 1 of the pelvis, and 1 of the ribs), and 3 were medical cases in which the embolism arose more or less *de novo*.

TABLE II

SEVENTY CASES OF HEART DISEASE WITH EMBOLIC INFARCTS

Certifiable Cause of Death	Number of Cases				
	Total	With Congestive Failure	With Major Embolism *	Clinical State	
				Bed-ridden	Ambulatory
Rheumatic heart disease	27	25	21	20	7
Coronary disease ..	27	18	18	19	8
Other cardiopathies	16	9	8	12	4
Total	70	52	47	51	19

* Pulmonary embolism severe enough to be entered on the death certificate as a contributory cause of death.

The interval between operation and death varied from three to seventeen days and averaged eleven days. In the fracture cases the interval averaged twenty-two days. Infarction of the lung is not uncommon in deaths from pulmonary embolism after operation or after trauma, and indicates, as a rule, that smaller emboli have preceded the fatal seizure by hours or days.

It was possible to find the *apparent source of the emboli* in 116 cases. Usually it was a thrombus in the veins of the pelvis or thigh. The actual figures, as shown in Table III, were: pelvic veins 52, leg veins 42, right heart 16, veins of upper extremity (including subclavian) 6.

In the pelvis the commonest sites were the peri-prostatic, the uterine, and the internal iliac vein ; in the thigh, the femoral and saphenous veins.

Seldom was the venous thrombosis accompanied by obvious phlebitis and this, of course, is a factor which tended to obscure the clinical recognition of embolism in many of our cases. Perhaps the commonest and most distinctive symptom recorded in the histories of these cases was the coughing up of blood, either as rusty sputum or as frank hæmoptysis. In addition, pleural pain and pleural rubs were frequently observed. Under such circumstances the infarction was commonly mistaken for pneumonia with pleurisy. Another common

symptom was a sudden attack of breathlessness, accompanied by cyanosis, anxiety, and sweating; and this was often put down to a sudden change for the worse in the function of the heart rather than to embolism.

TABLE III

APPARENT SOURCE OF EMBOLI

Certifiable Cause of Death	Thrombus in				
	Pelvic Veins	Leg Veins	Arm Veins	Right Heart	All Sites
Rheumatic heart disease	7	6	5	5	23
Coronary disease	11	8	—	5	24
Other cardiopathies	6	5	1	4	16
Pulmonary embolism	8	10	—	—	18
Malignant neoplasm	10	5	—	—	15
Pulmonary tuberculosis	1	3	—	2	6
Cerebral softening	4	3	—	—	7
Miscellaneous	5	2	—	—	7
All Causes	52	42	6	16	116

PRIMARY PULMONARY THROMBOSIS

The ten cases of pulmonary thrombosis were of miscellaneous origin and scarcely permit of generalizations. In two instances there was tumour invasion of the vessel wall and in a third an arteritis due to tuberculous disease of the lung. Three others had small thromboses as a concomitant of severe toxæmia. In the remaining four the thrombosis was probably attributable to antecedent embolism.

Endarteritis of the pulmonary arteries has often been cited as a cause of pulmonary thrombosis, but in my experience this is rare. What may sometimes be mistaken for endarteritis is an involutional change in a vessel wall beyond a point of embolic occlusion. It is something like the change that occurs in the umbilical artery after birth. The intima proliferates to a considerable thickness (Fig. 2) and might well be taken for endarteritic change, if one did not know the vessel had been rendered defunct by an embolus lying proximal to the point where the section was taken.

DISCUSSION

Virchow (1856) introduced the term embolus and first described the phenomenon of thrombo-embolism ; he said that ante-mortem clots in the

FIG. 2.—Intimal thickening in a pulmonary artery, distal to the point of embolic occlusion. This change, which is involutional, may be mistaken for endarteritis. Magnification, ×30. (Museum specimen, 152.25.2, B.P.M.S.)

pulmonary arteries were, in his experience, practically always embolic, and that their occurrence was an almost sure indication of older thrombus somewhere in the venous circulation. Others who have carried out large scale investigations on autopsy material have reached a similar conclusion (Lubarsch,1905; Møller, 1922). Ribbert (1902) seems to have been the chief protagonist of the alternative view. His grounds for dissent seem somewhat obscure, but he denied the importance that Virchow attached to embolism and held the majority of pulmonary clots to be formed *in situ*. Ribbert's teaching became firmly established in the minds of many of his followers and to this day it is not easily shaken. My former chief, the late Professor Oskar Klotz, was one of Ribbert's students, and it was only after painstaking examinations in a large series of autopsies (Belt, 1934) that he became convinced of the relative frequency of embolism.

One would find it difficult to decide between the conflicting views of Virchow and Ribbert without putting the matter to an actual test. The important point is : What are the criteria by which an embolus may be recognized ? There are perhaps no hard-and-fast criteria, and those which have been set down here may be as arbitrary as any yet devised. On paper one can but convey a general impression of how an embolus is identified ; in practice it becomes relatively easy provided a satisfactory dissection of the pulmonary arteries is carried out.

If, as we suppose, 85 per cent. or more of lung infarcts are due to embolism,

then the problem of ætiology is largely a consideration of venous thrombosis, and that is a matter which remains obscure. In another place (Belt, 1939) I have indicated that most cases of thrombo-embolism present evidence of a prolonged circulation time, and I have emphasized again the mechanical factors to which Aschoff drew attention years ago—stasis, stagnation, and eddying—as important in the causation of the embolizing type of thrombus.

Summary

In 1990 consecutive autopsies on adults, there were 155 cases of hæmorrhagic infarction of the lung. Pulmonary embolism was regarded as the immediate cause of 136 (approximately 87 per cent.) of these infarcts.

In 22 (14 per cent.) a massive pulmonary embolism was the main diagnosis, and most of these were after operations or fractures. In 74 (47 per cent.) heart disease appeared to be a predisposing factor.

A potential source of emboli was demonstrated in 116 (75 per cent.) of the infarct cases.

Means of identifying emboli at autopsy are discussed, and evidence adduced to show that embolism of the pulmonary arteries is of very common occurrence, while primary pulmonary thrombosis is relatively rare.

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Note by the Editor

A recent paper by H. J. Atkins (*Guy's Hospital Reports*, **88,** 92, 1938), dealing with post-operative thrombosis and embolism, reaches the same conclusion that pulmonary infarction is nearly always caused by embolism from venous thrombosis. He finds that massive embolism may occur any time in the first fifteen days, most often about the tenth day ; and that it is independent of sepsis, and therefore depends on the stagnation of the blood stream, especially from the mechanical conditions of rest. Smaller infarcts

are more closely associated with sepsis (which suggests that the embolism is more often due to the breaking off of a small part of the thrombus), and are more erratic in the time of their appearance. He emphasizes the importance of the pressure of the right common iliac artery on the left common iliac vein in producing the thrombosis. His figures cannot be given in detail here, but are interesting in comparison with the relevant figures of Belt.

HERPES ZOSTER AND ANGINA PECTORIS

BY

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Received May 18, 1939

Substernal pain on effort is recognized as one of the manifestations of disease of the coronary arteries. However, in recent years, clinicians have come to recognize the coronary nature of attacks in which pain is absent or minimal. That pain of cardiac origin is not necessarily paroxysmal has also been suggested, while occasionally painless sysmptoms have been recognized to accompany or even to replace true anginal pain. In a future paper the authors propose to describe such phenomena and consider their significance. In this communication we shall consider one such phenomenon, namely, herpes zoster, and its occurrence in patients with angina pectoris.

Several observers have noted the occurrence of herpes zoster in patients suffering from periodic bouts of anginal pain. A study of the case histories in Head's (1900) classical report on herpes zoster revealed that one of his patients was suffering from anginal paroxysms. He was a man of 35 years, with weakness and cough of two years' duration and severe attacks of pain over the heart. Herpes zoster developed over his chest on the right side, at the level Th. 7, one week before his entry to hospital. He died on the following day during a severe anginal attack and at autopsy proved to have extreme atheroma of the aorta, with aortic obstruction and regurgitation, and an enlarged left ventricle. No mention was made of the coronary arteries. The right Th. 7 ganglion was profoundly affected, riddled with extravasated blood and round-cell infiltration. Head did not consider the possible significance of the association of the two conditions. Osler, in his Lumleian lectures on angina pectoris (1910), mentioned a patient who developed herpes zoster along the track of the anginal pain he had felt periodically for the previous ten years ; it was the only such case that Osler had witnessed. Allbutt (1915) observed two cases in which the conditions were associated and wrote, " In the case of a lady (suffering from angina pectoris) who arrived at my house after an attack (of herpes zoster), the left arm had to be gently borne on a pillow by her maid as she passed from the carriage to the house."

With one exception, remaining references on this subject are of German origin. In Ortner's patient (1911) the zoster was distributed over the area subserved by the left ulnar nerve, Th. 1 ; such a distribution is uncommon

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(Head, 1900). The patient had been suffering from genuine angina pectoris for some time and the pain radiated down the ulnar aspect of the left arm in attacks. Autopsy showed intense sclerosis of the coronary arteries without evidence of syphilis of the aorta or elsewhere. Fehsenfeld (1921) has described a similar case. Arnstein (1921, 1922) observed the association of herpes and angina, and in a paper entitled "Herpes zoster as the only manifestation of affections of internal organs running an otherwise latent course" concluded that zoster is frequent with disease of the lungs, liver, and kidneys, while rare with digestive, genital, and heart disease. He observed that its location usually corresponded with the organ affected. In one patient with marked sclerosis of the abdominal aorta attended with paroxysms of severe colicky abdominal pain, herpes zoster appeared over the left upper quadrant. Wertheimer (1927 and 1928) reported two patients with paroxysms of angina pectoris, of one and eight years' duration respectively, who developed herpes zoster over the area of radiation of substernal and arm pain. In one it occupied segments Th. 1–4 anteriorly and posteriorly on the left side, and segment Th. 1 on the left arm. In the second the arm was not involved by the rash, but the thumb and index finger of the left hand began to show diminished sensibility to pain. Parsonnet and Hyman (1930) have recorded three interesting cases in which recurrent attacks of herpes zoster were associated with the simultaneous development of symptoms and signs of progressive coronary disease, as evidenced by typical anginal seizures, electrocardiographic changes, and ultimate sudden death in all three. Previous to the first bouts of herpes zoster there were no cardiac symptoms or signs and electrocardiograms taken at the time of the herpes attacks proved normal.

We have encountered 12 instances of herpes zoster in a series of 350 patients with angina pectoris. In 10 instances the zoster appeared after the anginal attacks had become established, while in 2 the zoster preceded the angina. In the latter (Cases 11 and 12) the zoster first appeared before the first anginal paroxysm. In Case 11 the subsequent anginal pain involved the right shoulder and arm, where the zoster rash had appeared two and a half years before. In Case 12 there were recurrent attacks of herpes zoster over the left chest in the eighteen months preceding the first anginal attack. In the remaining 10 cases the anginal pains had been experienced first, in all but one for several years, and in the majority were severe and frequent.

The main features of these 12 cases are outlined in Table I. The majority of patients were elderly, 8 being over sixty years of age. All suffered from true angina of effort, relieved by nitrites, except one (Case 10), who had a syphilitic aneurysm of the ascending limb of the arch of the aorta with much substernal and left arm pain. The Wassermann and/or the Hinton reactions were negative in the remainder, and none gave a history of luetic infection. Electrocardiograms, taken in six cases, all showed evidence of coronary insufficiency.

In Figs. 1 to 12 are outlined the distributions of the referred cardiac pain and herpetic eruption in the 12 patients, and short histories follow. In 10 cases a fairly close segmental relationship is apparent between the two areas. In

Case 6 the cardiac pain was referred to the right shoulder and arm (C. 5, 6, 7, 8 and Th. 1, 2, 3) while the eruption appeared over the left shoulder (C. 4). In Case 9 the anginal pain was very severe and widespread ; it radiated to both shoulders and arms and occasional paroxysms spread to involve the epigastrium, left upper quadrant of the abdomen and the left infrascapular region. The eruption commenced on the anterior aspect of the left thigh and spread upwards over the left inguinal and gluteal region to involve the left lumbar area (Th. 9, 10, 11, 12 and L. 1 and 2).

TABLE I

HERPES ZOSTER AND ANGINA PECTORIS

Case Number	Age in Years	Number of Years with Angina before the Onset of Herpes	Site of Anginal Pain	Severity of Angina	Frequency of Angina	Distribution of Herpes
1	74	4	Substernal to R. and L. upper chest	XXX	Daily	Right : Th. 5, 6, 7. Anterior.
2	70	4	Præcordial to L. shoulder	XXX	Irregular Infrequent	Left: Th. 2, 3, 4. Anterior
3	67	6	Substernal to L. chest and shoulder	XX	Frequent	Left : Th. 2, 3, 4. Ant. and Post.
4	60	2	Substernal to R. chest	XX	Frequent	Right : Th. 6, 7. Ant. and Post.
5	54	5	Substernal	XX	Frequent	Left : Th. 5, 6. Ant. and Post.
6	83	12	Substernal to R. arm	XX	Frequent	Left : C. 4. Anterior.
7	70	$^1/_2$	Substernal to R. arm	XXX	Frequent	Right : C. 4, 5. Th. 1, 2, 3, 4. Anterior.
8	58	4	Substernal	XXX	Very frequent	Left : C. 5, 7, 8. Th. 1, 2. Anterior.
9	66	5	Substernal to both arms	XXX	Very frequent	Left: Th. 9, 10, 11, 12. L. 1, 2. Anterior.
10	42	5	Substernal to left axilla and neck	XX	Very frequent	Left : C. 4, 5, 6. Anterior.
11	49	*	Substernal to R. arm	XX	Frequent	Right : Th. 4, 5, 6. Anterior.
12	71	*	Substernal to L. arm	XX	Frequent	Left : Th. 4, 5, 6. Anterior.

XX signifies moderate anginal pain. XXX signifies severe anginal pain.

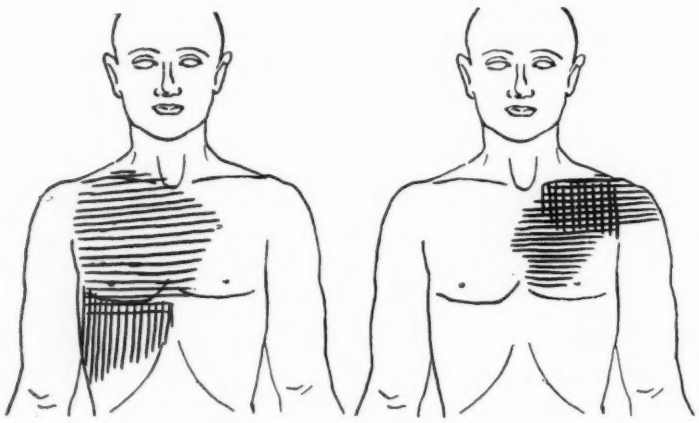
* In these two cases the herpes occurred $2^1/_2$ and $1^1/_2$ years respectively before the angina.

Case Histories

Case 1.

Male, aged 74. Left temporal headaches for five years. Four years dyspnœa on exertion and typical angina of effort, lasting a few minutes and relieved by rest or nitroglycerine. There was no actual radiation of the anginal pain to the left arm, but some numbness ; it spread to the upper chest on both sides, chiefly the right. About 8 months ago, when the angina was getting more frequent and severe, an herpetic eruption appeared over the right side of the chest anteriorly, Th. 5, 6 and 7. Its lowest limit was at the costal margin approximately. He became more short of breath about this time. Three months later increasing dyspnœa and œdema of the ankles. For the past two months the anginal attacks have increased in frequency and severity.

Examination : Heart enlarged to the left by X-ray. Systolic thrill and systolic and probable diastolic apical murmurs. Radial and brachial arteries firm and tortuous. Blood pressure 160/85. Moderate œdema of ankles. Tortuous aorta by X-ray. Electrocardiogram; rate 75, fibrillating, inverted T waves in all leads, left bundle branch block.



Case 1 Case 2

FIGS. 1 and 2.—Diagram showing the areas of distribution of the herpetic eruption and of the referred cardiac pain. The black horizontal lines indicate the area of the referred pain and the vertical lines represent the distribution of the herpetic eruption.

Case 2.

Male, aged 70. Well and active until four years ago, when first attack of præcordial pain on walking. Tends to recur on excitement or exertion. One year ago a severe attack without radiation to arms. Hypertension then present. Two months ago herpes zoster over the left chest and shoulder. Unable to continue his work as a butler thereafter.

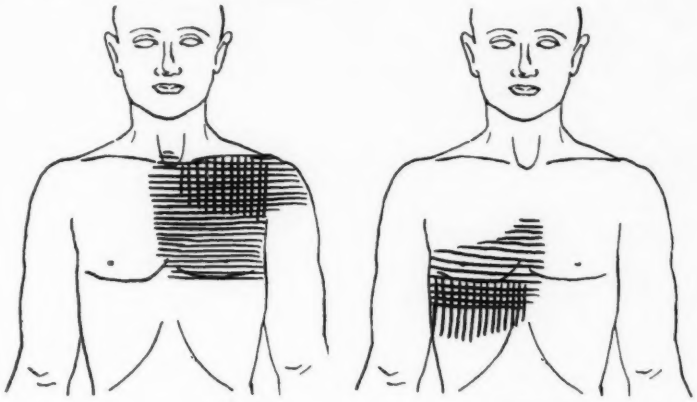
Examination : B. P. 180/90. Slight apical systolic murmur ; soft arteries ; liver edge felt one finger below costal margin ; slight œdema of ankles.

Case 3.

Male, aged 67. Six years headaches, palpitation, and weakness, and started to have dyspnœa and substernal distress on exertion : unable to walk any distance because of this. Three days ago severe persistent pain over left chest and shoulder, without

radiation to arm. Substernal distress on exertion was particularly marked and lasted ten minutes at a time.

Examination : Obese, moderate peripheral arteriosclerosis, heart enlarged to the left with a forcible apex beat. B. P. 215/145. Systolic apical murmur. Herpetic lesions in left axilla and over upper three left ribs anteriorly, and posteriorly over left scapula. Urine, albumen and granular casts.



Case 3 Case 4

FIGS. 3 and 4.—The black horizontal lines indicate the area of the referred pain and the vertical lines represent the distribution of the herpetic eruption.

Case 4.

Female, aged 60. Two years dyspnœa and occasional substernal pain on exertion. Two days ago sudden pain starting in the right costal margin and lower chest, radiating to the right costovertebral region. This pain persisted until admission to hospital.

Examination : Slight cyanosis. B. P. 160/70. Heart enlarged to left. Systolic and diastolic aortic murmurs. Wassermann negative. Electrocardiogram ; left axis deviation, sagging T_1 and T_2, slight late inversion of T_4, wide slurred QRS waves, deep Q_4, high S-T_4. Herpes zoster over the area of pain. The patient improved, but returned one year later with persistent angina. A third admission to hospital ten years later with moderate cardiac failure and severe anginal episodes.

Case 5.

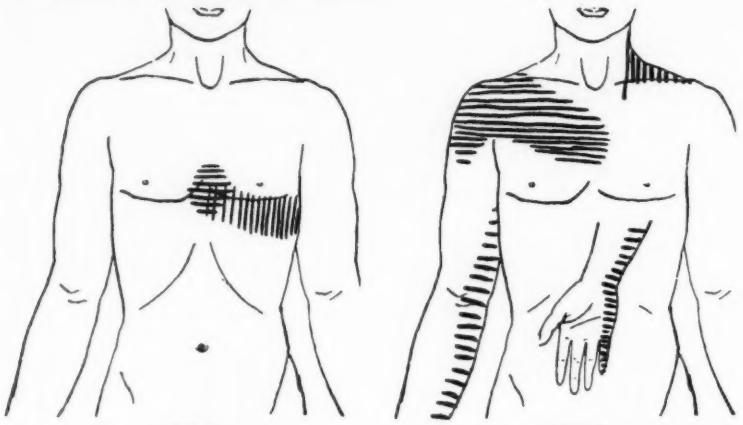
Female, aged 54. Five years ago frontal headaches and hypertension discovered. About the same time began to have substernal constriction on exertion. No radiation of pain to the arms. Attacks have persisted without much change. Five days ago superficial pain under the heart and round to the back, persistent and not in paroxysms as the anginal pain.

Examination : B. P. 260/120. Moderate arteriosclerosis. Heart enlarged to left. Blowing systolic præcordial murmur. Typical herpes over left præcordial region and at angle of left scapula. Hyperæsthetic.

Case 6.

Female, aged 83. Twelve years ago at the age of 71 severe pain in right upper chest, shoulder, and right arm on exertion. One year ago weakness and dizziness on exertion became prominent ; no præcordial pain at this time. Three days ago a typical herpes appeared over left shoulder.

Examination : Marked arteriosclerosis. B. P. 180/100. Heart enlarged to left. Apical systolic murmur. Herpetic eruption.

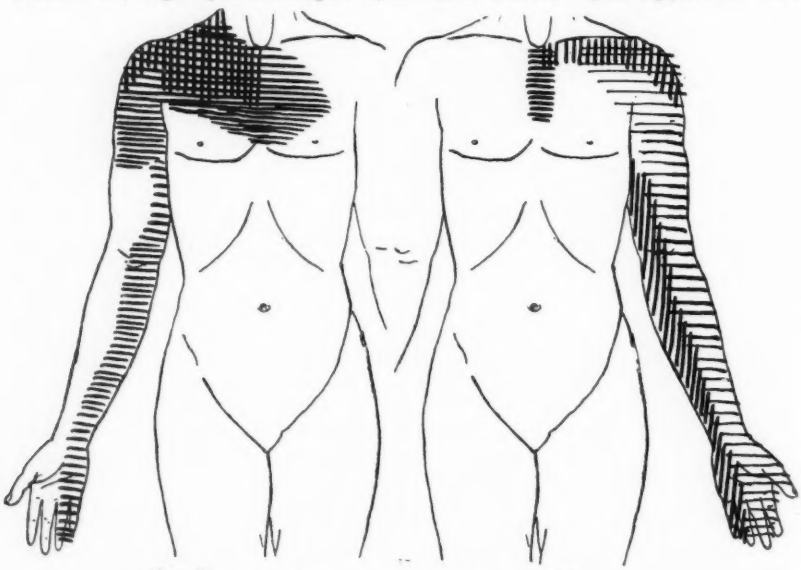


Case 5 Case 6

FIGS. 5 and 6.—The black horizontal lines indicate the area of the referred pain, and the vertical lines represent the distribution of the herpetic eruption.

Case 7.

Male, aged 70. One and a half years dyspnœa on exertion with discomfort and exhaustion ; angina pectoris diagnosed, and attacks relieved by nitroglycerine. One



Case 7 Case 8

FIGS. 7 and 8.—The black horizontal lines indicate the area of the referred pain, and the vertical lines represent the distribution of the herpetic eruption.

year ago herpes zoster over right arm, upper chest, shoulder, and neck ; still gets pain there at times, especially when resting. Six months ago typical anginal attacks with radiation of pain to the right shoulder and arm.

Examination : Poor, distant, heart sounds. Apical systolic murmur. Sclerosed radial artery. Rales at both lung bases ; liver edge tender, two fingersbreadth below costal margin ; no œdema.

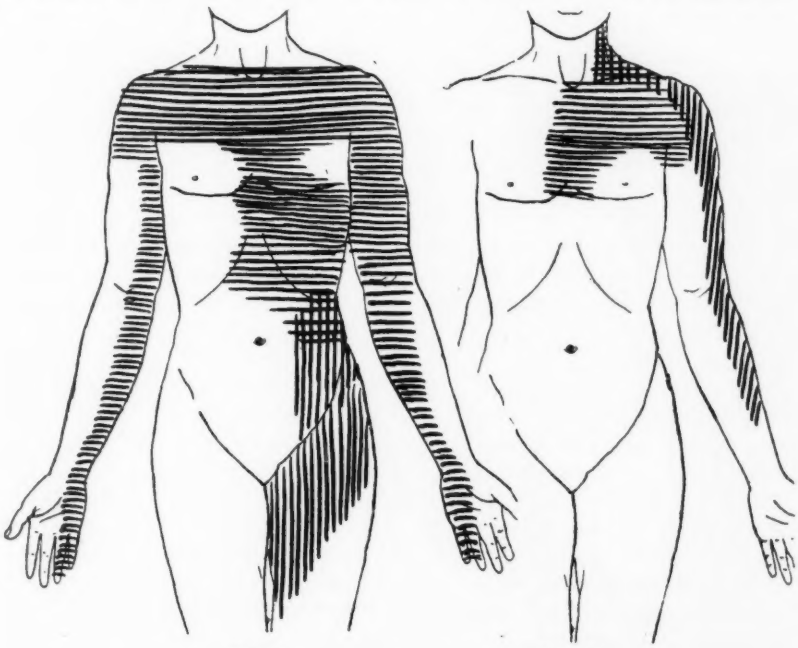
Case 8.

Male, aged 58. Four years ago midsternal pain on exertion, relieved by rest, or nitroglycerine. Increasing in frequency and severity. Three years ago in hospital : heart enlarged to left, with distant heart sounds. Rough apical systolic murmur with (?) diastolic aortic murmur. Liver just palpable. Electrocardiogram ; normal rhythm, low T_3, inverted T_4. Fairly well for the next three years. Last three months angina pectoris much worse, but still relieved by nitroglycerine. Two weeks ago more severe pain in left shoulder, radiating to the left arm and fingers. At first only present on exercise but soon became constant. Nitroglycerine ineffective. At this time the substernal anginal pain on exertion radiated to the left arm and left fingers, for the first time. No dyspnœa.

Examination : As before. B. P. 180/90. Typical herpes scattered over left shoulder and down the inner side of left arm to fingers. The painful area radiating from the sternum spread down the outer side of that arm. Gradual improvement.

Case 9.

Male, aged 66. Five years typical anginal attacks ; pain severe and widespread, to both arms, to epigastrium and left loin. Nitroglycerine gave prompt relief.



Case 9 Case 10

FIGS. 9 and 10.—The black horizontal lines indicate the area of the referred pain and the vertical lines represent the distribution of the herpetic eruption.

Typical gout for some years. Four days ago sudden sharp shooting pain in left side of lower chest, loin, and left thigh. This was quickly followed by an herpetic eruption.

Examination : Obese. Herpes as described. Heart enlarged to left ; premature beats ; apical systolic murmur. Moderate arteriosclerosis. Electrocardiogram ; diphasic T_1.

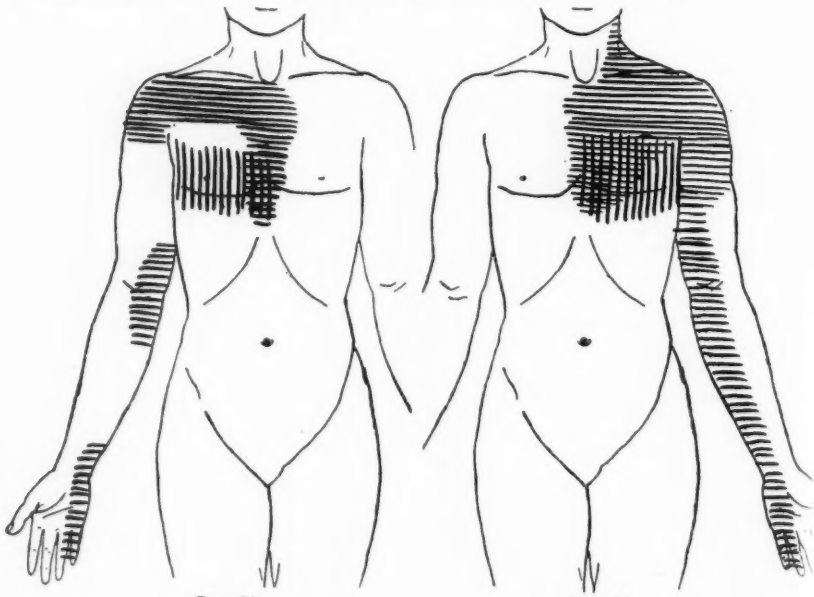
Case 10.

Male, aged 42. Five years præcordial pain with cough, dyspnœa, and dysphagia. Wassermann reaction positive. Aneurysm of aorta on X-ray. Treated with mercury and iodides. Now almost constant chest pain and anginal exacerbations. Aneurysm pointing in the suprasternal area. Two weeks ago hyperæsthesia over the left upper chest with severe, sharp, burning pain. Five days ago herpes zoster over left upper chest, axilla, and radial aspect of left arm.

Case 11.

Male, aged 49. Four years ago attack of herpes zoster involving the right chest and arm ; no sequelæ. Eighteen months ago some stabbing pain in left chest. Six months ago typical angina with pain down right arm. Attacks progressive and excruciating and one lasted for 36 hours.

Examination : Raised temperature and leucocytosis of 14,000. B. P. 115/70. Electrocardiogram ; inverted T_1 and T_4, wide slurred QRS waves. Following this myocardial infarction, recurrent anginal attacks. Heart slightly enlarged.



Case 11 Case 12

FIGS. 11 and 12.—The black horizontal lines indicate the area of the referred pain and the vertical lines represent the distribution of the herpetic eruption.

Case 12.

Male, aged 71. Recurrent attacks of herpes zoster over the left mid-chest region, front and back, during several years ; scars present under the left breast. Typical

attacks of angina pectoris for eighteen months beginning substernally and spreading to left upper chest, shoulder, and ulnar aspect of left arm. Attacks provoked by exercise, emotion, or a heavy meal ; four or five attacks daily of late.

Examination : Moderate peripheral arteriosclerosis. B. P. 160/100. Heart enlarged to left, fair heart sounds, no murmurs. Palpable liver edge. Tortuous aorta on X-ray examination. Electrocardiogram ; diphasic T_2 and T_3.

Discussion

Are these findings fortuitous or does the zoster reflect some change in the posterior root ganglia in anginal patients ? Having sifted the available evidence we lean to the latter explanation and suggest that the zoster is a trophic manifestation of continued irritation of the posterior root ganglia by impulses from the diseased viscus. Our evidence may be marshalled as follows.

As we have pointed out, the phenomenon has been recorded previously. The discovery of twelve examples among our own records is significant. A rapid control perusal of a large number of case histories of congestive heart failure revealed no example of herpes zoster in the same age group. The similarity between the relative areas of distribution of the referred cardiac pain and the herpetic rash is so striking in several instances that coincidence seems highly improbable. In Case 7 (Fig. 7) both were distributed over the right upper chest and inner aspect of the right arm. As pointed out by Head, herpes zoster only rarely involves the upper limbs.

Secondly, several reports have been published of the appearance of herpes zoster over the distribution of referred pain in other diseased conditions. Moreover, pain was an outstanding feature in all these, viz. biliary colic, renal colic, abdominal colic, pleurisy, pericarditis, appendicitis, and arthritis. Curtain (1902) has observed the appearance of herpetic eruptions over an acute arthritic knee joint, over the area of pain and friction in a dry pleurisy, over an area of localized peritonitis, and over the left kidney during a bout of hæmaturia. Bittorf (1911), Rosenbaum (1911), Kanera (1911), Rosenberg (1911), and Krotoszymer (1911) have described instances of the appearance of herpes zoster over the homolateral segments, Th. 10 or Th. 10 and 11, in cases of renal colic due to calculus or intermittent hydronephrosis. Severin (1926) observed two similar cases and one in which the herpes rash appeared over segment Th. 9 on the right side in a case of gallstone colic. In patients suffering from gastric colic with hypermotility of the stomach observed by fluoroscopy, Hess and Faltitschek (1925) described the appearance of herpes zoster over the lower thoracic segments. The gastric disturbances disappeared with the subsidence of the eruption. Lastly, Loeper and Loisel (1937) reported the occurrence of herpes zoster over the area of referred pain (C. 4, Th. 1 and 2) in acute rheumatic pericarditis. On the ninth day of an attack of acute rheumatism their patient, who was suffering from pericarditis, with a friction rub, developed an herpetic eruption, which disappeared with the exhibition of salicylates and the subsidence of the pericarditis.

The crises of pain in tabes dorsalis are sometimes attended by the develop-

ment of herpes zoster. In recurrent gastric crises the zoster may make its appearance along the costal margin (Udaondo, 1928 ; Laignel-Lavastine and Boquien, 1932) and may appear over the legs following paroxysms of lightning pains. The known involvement of the root ganglia in this disease probably accounts for such phenomena, and may have been the reason for the outbreak of herpes zoster in our example with a syphilitic aneurysm (Case 10).

Thirdly, our contention gains support when it is recalled that other skin lesions have been observed along the line of radiation of pain in angina pectoris. Mackenzie (1893) recorded a case in which, following a series of rapidly recurring anginal attacks with radiation of pain down the left arm, a streak of ecchymoses, six inches in length, developed on the left arm without obvious cause, and was assumed to be trophic. That such a lesion probably resulted from disturbance in the thoracic posterior root ganglia is suggested by the known occurrence of similar ecchymotic areas along the path of the lightning pains of tabes dorsalis ; in the latter condition we know these ganglia are involved. Allbutt (1915) quoted two patients described by Gasne and Chiray (1905) ; both suffered from typical angina pectoris and both developed a peculiar rash resembling lichen planus along the areas of referred pain. In both it spread along the ulnar aspects of arm and forearm, and in one it involved the left chest wall also.

Admitting for the moment, then, that the appearance of the herpes zoster is in some way related to the second pathological condition present, viz. ; disease of the coronary arteries, we may consider by what possible mechanism this can be brought about. Herpes zoster may be due to invasion of the posterior root ganglia by a specific virus, and involvement of the ganglia by adjacent disease processes can produce the condition. Leucæmic infiltration, Hodgkin's disease, tumours, and syphilis may act in such a manner. It is perhaps not widely known, however, that there is evidence that it may result in a reflex manner following repeated irritation of the ganglia by impulses from a diseased viscus. Head and Campbell (1900) wrote " the trophic disturbance of the skin is an extreme form of activity of the same cells, disturbance of which by afferent impulses along the white ramus produces the hyperalgesia that accompanies visceral and referred pain. . . . The eruption is due to intense irritation of cells in the ganglion which normally subserve the function of pain, and more particularly that form of pain produced by afferent visceral impulses. . . . Some ganglia seem more prone to attack than others. . . . the ganglia most commonly affected are those which receive afferent impulses from the viscera."

Gaule (1894) was among the first to produce trophic changes in the skin of experimental animals by stimulation of the ganglia. He especially noted that these trophic effects were by no means confined to the segment served by the stimulated ganglion, but spread to the opposite side and over the whole body. This is of interest in view of our findings in some cases that the herpes may appear in adjacent segments, or even, as in Case 6, on the opposite side.

Krogh (1924) during his investigations on the physiology of human capillaries wrote " In herpes zoster we have evidence that a large number of capillaries

. . . are in direct connection with posterior root fibres and become dilated when these are stimulated . . . by pathological processes."

Lewis and Marvin (1927), in like vein, concluded that the probable explanation for herpes zoster was that antidromic impulses released a histamine-like substance in the skin area of that segment, with capillary dilatation and blister formation. They suggested the mechanism was thus a modified triple response ; the period of stimulation is prolonged and the wheal is replaced by a blister.

For these reasons, then—the repeated clinical observation of herpes zoster in anginal patients, the analogy of the herpetic eruption in other painful visceral states, the occurrence of other skin lesions along the line of radiation of anginal pain, and the existence of an anatomical nervous pathway between ganglion and skin that can conduct antidromic impulses—it is reasonable to conclude that the appearance of herpes zoster over the area of referred pain in anginal patients is not fortuitous. It signifies the repeated bombardment of spinal root ganglia of the thoracic cord by afferent impulses from the diseased heart.

Summary and Conclusions

We have described twelve instances of the occurrence of herpes zoster in anginal subjects. In ten of these the zoster appeared after the anginal attacks had become established. In two the zoster first appeared about two years before the first anginal paroxysm. In both these, as in the former group, a close association was apparent between the distribution of the herpetic eruption and that of the anginal pain.

Attention has been drawn to the occurrence of herpes zoster over the area of referred pain from other diseased viscera also, viz., the pleura, pericardium, gall bladder, kidneys, stomach, and appendix. We have suggested that repeated bombardment of spinal root ganglia by afferent impulses from the ischæmic heart gives rise to antidromic impulses that lead to vasodilatation and blister formation in referred cutaneous areas. The herpetic eruption is thus a trophic manifestation of disease of the coronary vessels in these cases.

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SEX AND AGE FACTORS IN ACUTE AND CHRONIC VALVULAR DISEASE

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Received May 26, 1939

In a pathological study of cardiac disease in pregnancy, controls were needed from women of child-bearing age who were not pregnant. This raised the question of the influence of the sex or age of patients on the various aspects of valvular disease. It is, however, difficult to get satisfactory pathological information on this point. Clinical studies of these factors have been made by Gillespie (1898), Andrew (1909), MacDonald (1914), and Willius (1926); some pathological details are included, but they are inadequate for the present purpose. The accuracy of clinical diagnosis of chronic valve lesions is a little over 50 per cent., as shown by Cabot (1926) and Frey (1936), so that the information from clinical studies about the sex and age differences of the valve lesions is not sufficiently reliable. There are certain relevant pathological data in the papers of Cabot (1914 and 1926), Coombs (1924), and Cowan and Ritchie (1935), which are discussed later, but much of the information we required is not given by these authors.

An analysis was therefore made of the records of 11,700 consecutive autopsies in two large general hospitals and one children's hospital in Glasgow, the numbers of males and females being approximately equal. In these cases clinical and pathological details were abstracted of the 1057 patients that showed post mortem any chronic or acute valve lesions, excluding minor senile changes in the aortic valve. The few patients in these general hospitals who died during pregnancy or within eight weeks of delivery are excluded from this control series.

No investigation has been made of the microscopic appearances of the valves or heart muscle, so this limits the scope of our figures to lesions which are obvious to the naked eye. Certain of the pathological and clinical records may be incomplete, but this source of potential error appears insufficient to vitiate the general conclusions. No attempt has been made to assess the severity of the mechanical defects of the valve, a severe mitral stenosis and an incompetence due to minor scarring both being classed as chronic mitral lesions.

* Working with the aid of the Medical Research Council and the Robert Jardine Research Scholarship.

The valve lesions are considered under the headings of :

I. Chronic valve lesions, i.e. scarring of valves that is apparently of rheumatic type.

II. Recurrent endocarditis, i.e. simple acute vegetations on old scarred valves or on valves that were previously healthy in a heart with old chronic valvular disease.

III. Simple acute endocarditis, i.e. vegetations of rheumatic type in a heart without recognizable chronic lesions.

IV. Ulcerative or subacute bacterial endocarditis, whether on previously damaged valves or not.

V. Lesions of the aortic valve, either syphilitic or of the senile variety classed as primary sclerosis.

I. CHRONIC VALVE LESIONS

Excluding aortic lesions due to senile sclerosis or syphilis, 629 patients had scarring of one or more valves, producing stenosis or incompetence, and of the type usually accepted as due to old rheumatic involvement. Often there was a superadded simple acute or ulcerative endocarditis ; these will be discussed later.

The incidence of chronic rheumatic valvular disease was much higher in adults than in children. There were 596 cases in 7000 necropsies on patients aged 12 and over (8·5 per cent.), but only 33 out of 4700 in children under 12 (0·7 per cent.). These figures are slightly higher than those of Davis and Weiss (1932), who found 222 out of 3951 necropsies on patients 10 years old and over (5·6 per cent.) and only 4 out of 821 in children under 10 (0·5 per cent.).

Sex and Age Differences

The distribution of chronic lesions on the different valves has been studied by various authors (Edens, 1929), but no differentiation with regard to sex or age is found in their data, except in the work of Cabot (1926), who gives details of 208 patients.

In the present series the sex and age incidence of chronic lesions affecting (*a*) the mitral alone, (*b*) the aortic and mitral together, and (*c*) the aortic-mitral-tricuspid or the mitral-tricuspid, are plotted in Figs. 1 and 2 ; the number with each valve lesion being shown as a percentage of the total with any chronic valve lesion in the given age group and of that sex. The main points shown are the high relative incidence of aortic-mitral lesions in males, and of pure mitral lesions or of multiple valve lesions involving the tricuspid in females.

The number of cases is shown in Table I. From these it will be seen that the incidence of pure mitral and of mitral-tricuspid lesions is much greater in females than in males ; nearly three times up to the age of 25, and nearly twice over that age.

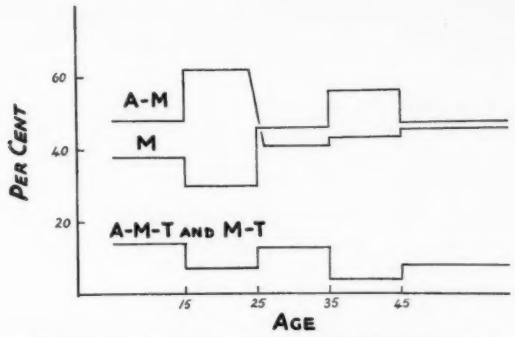

FIG. 1.—Percentage distribution of chronic valve lesions at different ages in males. M denotes mitral lesions ; A-M, combined aortic and mitral lesions, etc.

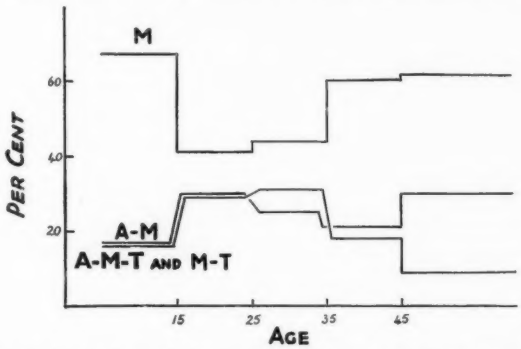

FIG. 2.—Percentage distribution of chronic valve lesions at different ages in females (see Fig 1).

TABLE I

SEX AND AGE INCIDENCE OF CHRONIC VALVE LESIONS

Sex	Age	M *	A-M	A-M-T	M-T	A	Others
Males ..	to 15	8	10	3	0	3	P-T
	16 to 25	9	19	1	1	3	P-T
	26 to 35	18	16	4	1	8	0
	36 to 45	26	21	1	1	12	0
	Over 45	44	45	5	3	16	A-M-P
	Total	105	111	14	6	42	3
Females ..	to 15	24	6	3	3	1	0
	16 to 25	18	13	7	6	3	0
	26 to 35	21	12	9	6	1	0
	36 to 45	41	14	7	6	5	M-T-P
	Over 45	84	41	8	4	4	0
	Total	188	86	34	25	14	1

* In this and all tables, M, A, T, and P stand for mitral, aortic, tricuspid and pulmonary valve lesions, and A-M, etc., for combined aortic and mitral lesions, etc.

On the other hand, a combined aortic-mitral lesion, including those with aortic-mitral-tricuspid involvement, shows the same absolute incidence in males and in females at every age group. The relative incidence is, however, higher in males.

The tricuspid is involved nearly three times as often in females as in males. A pure tricuspid lesion has not been observed ; it is more commonly associated with aortic-mitral than with mitral lesions. The two pulmonary-tricuspid lesions in young males were, as usually, associated with congenital heart disease.

Pure aortic lesions are rare in females but much commoner in males, particularly over 25, though some lesions in older males are open to the suspicion of being really due to primary sclerosis or syphilis.

Cabot (1926) noted the same predominance of mitral lesions in females and of aortic lesions in males. He found the aortic-mitral lesion more common in males than in females, but this is not striking in the present series if aortic-mitral-tricuspid is included with aortic-mitral disease.

Age at Death

The age at which patients die with various chronic valve lesions is about the same for pure mitral and for combined mitral and aortic lesions (Table I). On the other hand, patients with a tricuspid lesion superimposed tend to die much earlier, usually before the age of 35. The age of death with each valve lesion showed no essential difference between the sexes. Cabot (1926) considered that males tended to die earlier from mitral or combined lesions than females ; this does not agree with the present data.

Mode of Death

This is of importance not only with regard to the chronic valve lesion, but also with regard to the incidence of recurrent endocarditis. Clinically the patients have been classified into the following six groups according to the manner of death.

Progressive Failure.—Patients with typical congestive heart failure, with the usual signs becoming gradually worse until death ; post mortem, chronic venous congestion of the lungs and abdominal viscera, and usually pulmonary infarcts ; no clinical or pathological evidence of any complicating disease.

Failure Combined with Other Illnesses.—Patients with typical congestive failure, combined with pathological evidence of some complicating disease. In some the major factor causing death was the failure, in others the intercurrent disease ; a few have been included that died of sudden heart failure, apparently without any gross congestion previously.

Acute Rheumatism or Chorea.—Patients with acute rheumatism or chorea at the time of death or during the previous six months. The expression " acute rheumatism " is used to indicate rheumatic fever, and does not include growing pains, sore throats, or tonsillitis. Many of the patients in this group died with clinical and pathological evidence of failure, but they are not included in the first two groups.

Intercurrent Illness.—Patients with no history or post-mortem evidence of failure, who died from other illnesses such as pneumonia or carcinoma, excluding rheumatism.

Sudden, Violent Death.—Patients that died suddenly as a result of street accident or suicide, nearly half of them before the age of 45. Apart from having old scarred valves, they appear to have been in normal health.

Ulcerative Endocarditis.—All patients with any chronic valve lesion in whom a superadded ulcerative endocarditis was found at death. Some died of failure, others of septicæmia or intercurrent disease ; but all have been excluded from the previous groups.

Relation of Valve Lesions to Mode of Death

When the patients are considered according to the valves affected by the chronic lesion, there are certain striking differences in the mode of death. The actual numbers are shown in Table II. The chief points are the low incidence of failure in men with pure mitral lesions, the high incidence of failure in tricuspid lesions, and the high incidence of ulcerative endocarditis in chronic aortic lesions.

TABLE II

Type of Death with each Chronic Valve Lesion

Sex	Type of Death	M	A-M	A-M-T and M-T	A
Males	Failure, simple and combined, and rheumatism	41	62	18	13
	Intercurrent disease and violence	56	33	1	14
	Ulcerative endocarditis	9	16	1	15
Females ..	Failure, simple and combined, and rheumatism	117	54	55	5
	Intercurrent disease and violence	56	25	3	5
	Ulcerative endocarditis	14	7	2	6

The more important age differences are that 80 per cent. of the deaths due to intercurrent disease without failure were in patients over 35, and that the ulcerative aortic lesions were commoner among the older men.

Cabot (1926) observed death from failure in only two thirds of his chronic tricuspid cases, which is less than in the present series, apparently because only one of his seveu patients with mitral-tricuspid lesions had failure. In the present series there were 31 patients with mitral-tricuspid lesions, of whom 20 died of pure, and 6 of complicated failure.

II. RECURRENT ENDOCARDITIS

Of the 629 cases with chronic rheumatic valvular lesions, 71 had a superadded ulcerative endocarditis (see later). In the remaining 558, 244 had simple acute

vegetations, either on the scarred valves or, less frequently, on previously undamaged valves. This is referred to as recurrent endocarditis. This incidence of recurrent endocarditis in 46 per cent. of the chronic cases is in reasonable agreement with the findings of previous workers, whose combined data on 710 cases give an incidence of 40 per cent. : Gerhardt (1913), Coombs (1924), Cabot (1926), Clawson, Bell, and Hartzell (1926), Stone and Feil (1933), and Cowan and Ritchie (1935).

Pathologically the vegetations are indistinguishable from those of the various forms of simple acute endocarditis, and appear to have essentially the same ætiological factors. But they are much more liable to develop in a previously damaged heart than simple endocarditis in a normal one. This matter is well discussed by Gross and Friedberg (1936). It is difficult to form any good estimate of the age of the recurrent vegetations. Clinically they cannot be diagnosed during life except by inference, and generally are not recognized till after death. Histologically they are hyaline or fibrinoid masses of from 1 to 4 mm. in height, sometimes with, and sometimes without organization at their base ; while organization certainly indicates advancing age of the lesion, the rate at which it progresses in this situation is unknown.

Cause of Death

The chief data on the incidence of recurrent endocarditis are shown in Table III, divided into sections according to the various clinical factors.

TABLE III

Relationship of Recurrent Endocarditis to Age and to Type of Death

Age	Progressive Failure		Failure Combined		Acute Rheumatism		Intercurrent Illness		Violent Death	
	Total Chronic	Recurr. End.	Total Chronic	Recurr. End.	Total Chronic	Recurr. End.	Total Chronic	Recurr. End.	Total Chronic	Recurr. End.
To 15	29	25	2	1	26	21	0	0	0	0
16 to 25	37	22	8	6	14	14	9	4	4	0
26 to 35	43	20	9	7	5	5	22	11	3	0
36 to 45	52	20	14	6	3	0	46	13	2	0
Over 45	87	36	33	11	2	1	98	20	10	1
Total	248	123	66	31	50	41	175	48	19	1

Progressive Failure.—Fifty per cent. of these cases had a recurrent endocarditis. This high incidence appears significant, though it is not clear whether the recurrence is due to the failure, or whether it indicates a carditis which caused the failure. Most patients before the final cardiac failure have temporary failure and recovery several times, when it seems probable that acute vegetations are frequently present. Davis and Weiss (1931) also noted the high incidence of acute vegetations in patients who died of failure, but they did not give figures. Gerhardt (1913) found recurrent endocarditis in 11 out of 23 cases with failure.

Failure combined with Other Illnesses.—Recurrent endocarditis was found in forty-seven per cent. of the cases, practically the same figure as in the pure failure group.

Acute Rheumatism or Chorea.—Eighty-two per cent. of the cases with acute rheumatism at the time of death or during the previous few months had recurrent lesions. But there are a certain number, particularly children, with no recurrent vegetations, though these are to be expected with active rheumatism. Karsner and Bayless (1934) in a study of hearts with Aschoff nodes found recurrent endocarditis in 39 of 51 cases with old valve lesions. The data given by Rothschild, Kugel, and Gross (1934), and by Werner (1936) with regard to the incidence of active infection of the heart in rheumatic fever cannot be compared with the present figures, as they did not deal with the incidence of acute endocarditis. Acute rheumatism is not usually fatal, and probably most cardiac patients who have subsequent attacks of acute rheumatism develop a recurrent endocarditis at these times.

Patients who gave a history of acute rheumatism many years previously did not show any striking incidence of recurrent endocarditis, when due regard was given to sex, age, and manner of death. This agrees with Frey (1936), who also points out that its incidence diminishes with the passage of time since the last attack of acute rheumatism.

Intercurrent Illnesses excluding Rheumatism.—Twenty-seven per cent. of these cases had a recurrent endocarditis. The intercurrent disease that caused death was often of a type such as pneumonia from which recovery is usual. Thus it appears probable that, during passing illnesses, many patients with old valvular disease develop a recurrent endocarditis which is not clinically recognized and heals later. There is no clear evidence as to whether this is due to a flare up of a quiescent rheumatic infection in the heart or to a new infection due to the intercurrent disease. These diseases were of the same types and were found in the same relative proportions in recurrent endocarditis as in simple acute endocarditis in patients with hearts previously normal, who had died of intercurrent disease. The outstanding difference was in the incidence of the acute vegetations ; they were found in 27 per cent. of the patients who had old chronic valvular disease, and only in 1·5 per cent. of 10,643 patients with hearts previously normal.

The existence of this group is in itself sufficient evidence that a recurrent endocarditis does not always cause failure.

Sudden, Violent Death.—Among the 19 cases with chronic valve lesions in this group, the only one with recurrent endocarditis was an old man. These figures are small, but give no support to the theory that, in a person with an old valvular lesion but otherwise in good health, there may be frequent recurrent endocarditis without any exciting factor. This conclusion depends, of course, on the supposition that the vegetations are not rapidly evanescent.

Effect of Age and Sex

Age.—Running right across these clinical factors is the great variation due to the age of the patient. The percentage of patients in each age group who

TABLE IV

RECURRENT ENDOCARDITIS AT VARIOUS AGES

Age	Total Chronic Valve Lesions	Recurrent Endocarditis	Percentage
4 to 7	17	15	88
8 to 11	16	13	81
12 to 15	25	19	76
16 to 25	71	46	65
26 to 35	81	43	53
36 to 45	118	39	33
Over 45	230	69	30

showed recurrent lesions is given in Table IV. These are very close to the percentages given by Coombs (1924) from a study of 98 necropsies; his figures, which appear to be the only ones published, range from 88 per cent. under 10 years to 24 per cent. over 40 years of age. The high incidence of acute rheumatism and of death from progressive failure is probably responsible for the height of the figures in the earlier age groups, but there appears to be a true diminution in the incidence of recurrent endocarditis in older patients, quite apart from this. When the patients in each clinical group are considered separately, as in Table III, a similar steady reduction of the incidence of recurrent endocarditis with advancing age is obvious.

Sex.—There were 93 cases among 240 male patients with chronic valve lesions, and 151 cases among 318 females. It is, however, not satisfactory to compare the gross incidence of recurrent endocarditis in males with that in females without regard to the significant factors; the high incidence of acute rheumatism and of failure in females distorts the picture. When the cases are grouped on a clinical basis there is no obvious difference between the sexes except in the deaths from progressive failure (Table V). In this condition the incidence of recurrent endocarditis falls suddenly at about 15 years of age in

TABLE V

SEX DIFFERENCES OF RECURRENT ENDOCARDITIS IN DECOMPENSATION

Age	Males			Females		
	Total Chronic	Recurrent Endocarditis	Percentage	Total Chronic	Recurrent Endocarditis	Percentage
To 15 ..	10	9	90	19	16	84
16 to 25 ..	15	6	40	22	16	73
26 to 35 ..	20	6	30	23	14	61
36 to 45 ..	21	8	38	31	12	39
Over 45 ..	25	7	28	62	29	47

males, but not until about 35 in females. This sex difference is significant for the original purpose of this study, the provision of control figures for the investigation of cardiac disease in pregnancy.

Valves Affected

The valves affected by the acute recurrent vegetations are shown in Table VI, grouped according to the previous chronic valve lesion ; the figures show the actual number of cases with each lesion.

TABLE VI

Valves affected by Recurrent Endocarditis

Males

Recurrent Endocarditis	Chronic Valve Lesion					
	M	A-M	A-M-T	M-T	A	Others
None	63	53	7	3	20	P-T
M	**21**	11	2	1	0	A-M-P
A-M	4	**23**	2	0	0	0
A-M-T	5	3	**1**	0	3	0
M-T	0	0	1	**1**	0	0
A	3	3	1	0	**4**	0
Others	A-P	T, A-T	0	0	0	0

Females

Recurrent Endocarditis	Chronic Valve Lesion					
	M	A-M	A-M-T	M-T	A	Others
None	97	35	15	15	4	M-T-P
M	**43**	11	3	2	2	0
A-M	13	**21**	3	0	1	0
A-M-T	3	4	**3**	0	0	0
M-T	2	0	1	**1**	0	0
A	11	7	6	1	**1**	0
Others	A-M-P-T, A-T, A-M-P, A-M-P	A-T	T, A-T	T, T, T A-T, T-P,	0	0

Previously Fibrosed Valves.—Recurrence occurred on 36 per cent. of the 522 fibrosed mitral valves, on 35 per cent. of the 257 fibrosed aortic valves, and on 19 per cent. of the 79 fibrosed tricuspid valves. This rough proportion of 2 : 2 : 1 in the incidence of recurrence on mitral : aortic : tricuspid holds good for any subdivision of the cases according to sex, age, or mode of death, though the actual percentages are influenced by these factors. This relative immunity

of the tricuspid to recurrent endocarditis may be connected with the relative immunity of this valve to endocarditis in general.

These findings have a bearing on the question of recurrence on chronic lesions of multiple valves. In chronic aortic-mitral lesions the recurrence affects both fibrosed valves more frequently than one. In chronic mitral-tricuspid and aortic-mitral-tricuspid lesions recurrence on three or even two valves is much less frequent than recurrence on either valve separately.

Spread to Fresh Valves.—If there are fibrosed valves in a heart, the other healthy valves show a great tendency to develop an acute endocarditis, as compared with a heart in which none of the valves have been scarred (see Table VII). The valve incidence of this spreading endocarditis is about 3 : 3 : 1 for mitral : aortic : tricuspid, which is very similar to the 2 : 2 : 1 figure for recurrence on scarred valves. This proportion holds in all the clinical subdivisions. Generally this spread to fresh valves is associated with recurrent endocarditis on one or more of the scarred valves—46 of the 255 cases where there was a recurrent endocarditis. Occasionally, however, the acute endocarditis affects normal valves without any recurrence on the fibrosed valves—19 cases, 15 of which were women ; here the acute endocarditis affected only the aortic, and the fibrosed mitral or tricuspid had no recurrent lesions.

TABLE VII

RECURRENT ENDOCARDITIS SPREADING TO NEW VALVES

Non-scarred Valve	Hearts with Previously Damaged Valves			Hearts Previously Normal		
	Total	Spreading Endocarditis	Percentage	Total	Simple Acute Endocarditis	Percentage
Mitral ..	36	6	16·6	10,643	126	1·2
Aortic ..	301	46	15·3	10,643	82	0·8
Tricuspid..	479	25	5·2	10,643	12	0·1

Age and Sex Incidence.—A spread to new valves occurs most frequently with a pure chronic mitral lesion, as these patients have, of course, more unaffected valves than patients with multiple old lesions (a chronic aortic lesion of rheumatic type is relatively uncommon). Thus, as shown in Table VI, the spread is absolutely more frequent in females, in view of the higher number of pure chronic mitral lesions in that sex. When, however, the incidence is considered in relation to the number of cases in which spread was possible, there does not appear to be any significant sex difference in the valves affected. The age factor is much the same as in recurrent endocarditis, there being a gradual decrease in the proportionate incidence with advancing age.

The spreading lesion shows a relationship to the type of death similar to that of recurrent endocarditis in general ; it occurs in about one-third of the patients dying of acute rheumatism or of failure and in about one-seventh of the patients dying of intercurrent diseases.

III. SIMPLE ACUTE ENDOCARDITIS

Simple acute endocarditis is used here to mean any vegetations which are not obviously ulcerative or subacute bacterial, and where there is no chronic valve lesion macroscopically recognizable. As in recurrent endocarditis, the vegetations are small hyaline or fibrinoid masses about 1 to 4 mm. in height. It seems probable that they can develop in a few days, since they are sometimes found after quite short illnesses. A differentiation of these vegetations into rheumatic, as opposed to non-bacterial thrombotic or terminal, is made by some authors on the basis of the size and exuberance of the vegetations, as well as on the histology. While the non-rheumatic vegetations are sometimes large, the vegetations of all types are presumably small in the early stages, so no attempt has been made to subdivide the group on pathological appearances ; any subdivision here has been made on clinical grounds alone.

Though cases of ulcerative endocarditis have been excluded from this group, a few classified as simple acute endocarditis may really have been the early stages of the former. The difficulty of naked eye diagnosis is illustrated where there is a gross ulcerative endocarditis on one valve and also apparently simple vegetations on the same valve or on others. The co-existence of simple and ulcerative endocarditis on the same valve and the difficulty of differentiating them in the early stages by naked eye are discussed by Clawson and Bell (1926) and by Von Glahn and Pappenheimer (1935).

The numbers in the present series showing simple acute endocarditis are shown in Table VIII ; its rarity in children under 3 is referred to by Norris (1911) and de Vecchi (1931).

TABLE VIII

AGE INCIDENCE OF ACUTE ENDOCARDITIS

Age	Cases with Acute Endocarditis
To 3	4
4 to 7	14
8 to 11	14
12 to 15	11
16 to 25	15
26 to 35	13
36 to 45	23
Over 45	66

ÆTIOLOGY

The clinical conditions at or shortly before death are given in Table IX ; they are similar to those found with recurrent endocarditis in patients that die without failure.

Acute rheumatism or chorea is most frequently found in the young, and among these it is almost twice as common in females as in males.

The miscellaneous group includes pyogenic infections such as pneumonia, meningitis, and burns, and a variety of conditions such as toxic goitre and tuberculosis ; a history of acute rheumatism or chorea was not obtained in any

of these. Apart from a high incidence in young girls, there is no obvious sex difference. This group also includes three surprising cases, patients who were killed accidentally, and post mortem were found to have small vegetations on the aortic or mitral ; two were young adults. It is not possible to say whether there had been any minor illnesses, such as tonsillitis, before the fatal accident.

The remaining group of uræmia, hypertension, and carcinoma naturally provides most of the cases in later life. This type is usually referred to as terminal, and it is unlikely that any of these could have recovered. There is no obvious sex difference.

TABLE IX

ÆTIOLOGY OF ACUTE ENDOCARDITIS

Ætiological Factor	Sex	Age					
		To 15	16–25	26–35	36–45	Over 45	Total
Acute rheumatism or chorea	Male	11	1	0	1	1	14
	Female	15	3	1	1	2	22
Miscellaneous ..	Male	4	4	5	2	17	32
	Female	13	3	5	6	14	41
Uræmia, hypertension, or carcinoma	Male	0	2	1	4	19	26
	Female	0	2	1	9	13	25

VALVES AFFECTED

There is no difference between the valves affected by chorea and those affected by rheumatism : see Table X, where they are grouped according to

TABLE X

VALVES AFFECTED BY ACUTE ENDOCARDITIS

	Sex	M	A-M	A-M-T or M-T	A
To age 15					
Rheumatism	Male	3	4	4	0
	Female	5	9	1	0
Miscellaneous	Male	2	2	0	0
	Female	9	3	1	0
Over age 15					
Rheumatism	Male	0	2	1	0
	Female	3	3	1	0
Miscellaneous	Male	15	4	0	8
	Female	12	3	3	8
Uræmia, hypertension, or carcinoma	Male	7	6	1	12
	Female	18	2	0	5

ætiological factors. In children, most of the acute endocarditis is due to rheumatism, with the striking exception of pure mitral lesions in girls, which are more frequently *not* associated with rheumatism. Below the age of 15 rheumatism never causes an acute aortic lesion alone in either sex, but frequently an acute aortic-mitral lesion, particularly in girls. Over the age of 15, most of the acute endocarditis is not rheumatic in origin. After 35 there is a striking increase of pure mitral lesions, mainly in women, and also of pure aortic lesions, mainly in men.

IV. ULCERATIVE AND SUBACUTE ENDOCARDITIS

The term " ulcerative endocarditis " is used to cover not only the true ulcerative or malignant lesions but also subacute bacterial endocarditis of *Streptococcus viridans* type. The subject is well reviewed by Blumer (1923), Horder (1926), Thayer (1926), and Segal (1936). Though early ulcerative endocarditis may be hard to distinguish macroscopically from simple endocarditis, the fully developed, large, friable vegetations are quite characteristic. The cases included as subacute bacterial endocarditis are classified as occurring on previously damaged valves. They are selected on a pathological basis and not on the criterion adopted by Clawson, Bell, and Hartzell (1926) of a clinical history of over six weeks. This difference may account for the very high incidence of subacute endocarditis in certain American clinics, e.g. 60 per cent. of all hearts in which there was any valve lesion (Clawson, 1924).

It is not clear how often the ulcerative lesion begins as such or how often as a further development on previously simple acute vegetations ; there is a considerable weight of evidence that it may develop on simple recurrent endocarditis, as has been shown by Von Glahn and Pappenheimer (1935). It is of interest in this connection to note the great frequency of joint pains in the very early stages of the illness, without any septic arthritis, and before any recognizable embolic phenomena have developed.

Developing on Valves Previously Normal

Primary ulcerative endocarditis is relatively uncommon in children up to 11 ; in the present series there were 9 out of 4700 autopsies (0·2 per cent.), whereas over that age it was found 89 times in 7000 autopsies (1·3 per cent.). In adults the main point of interest is the biphasic incidence—very frequent up to 25, and then later, over 45. The cases in youth or early middle age were all septicæmic in origin or clinical course : over 45, about half were of septicæmic type, but the others were incidental findings post mortem in patients dying from other diseases—carcinoma of stomach, 8 cases ; other carcinomas, mainly of biliary tract, 5 cases ; uræmia due to prostatic enlargement or renal calculi, 6 cases ; miscellaneous conditions, 4 cases.

There is a slightly higher incidence in males than in females, related to differences in the valves affected : pure aortic lesions affected males almost exclusively ; the mitral was involved alone about twice as often as the com-

bined aortic-mitral; the pulmonary, which was hardly ever the site of simple endocarditis, was sometimes affected by the ulcerative lesion, particularly when there was a congenital basis or a spread to all the valves. None of the present cases appeared to be related to clinical gonorrhœa. There is no obvious valve difference between the septicæmic and the non-septic types. The numbers showing each valve lesion are grouped in Table XI according to sex and age. Some of the older patients may have had early senile changes in the aortic valve, which predisposed them to an ulcerative lesion, but this does not explain the high incidence of mitral lesions in the older men.

TABLE XI

ULCERATIVE ENDOCARDITIS ON NORMAL VALVES

	Age	M	A-M	A-M-T	A	Others	Total
Males ..	To 15	5	0	0	2	A-M-P-T; P	9
	16 to 25	5	2	1	5	P	14
	26 to 35	2	1	0	1	M-T-P	5
	36 to 45	0	1	0	5	0	6
	Over 45	14	5	1	4	A-T	25
Females ..	To 15	5	3	0	0	0	8
	16 to 25	4	5	0	0	A-T ; P	11
	26 to 35	4	0	0	0	M-T	5
	36 to 45	2	0	0	0	0	2
	Over 45	4	5	1	2	T	13

DEVELOPING ON PREVIOUSLY DAMAGED VALVES

In 42 per cent. of the 169 cases with ulcerative endocarditis a pre-existing chronic valve lesion was recognized, and possibly in some others the ulcerative endocarditis had destroyed any evidence of previous scarring. The frequency with which previously scarred valves are affected by ulcerative endocarditis is greater in males than females ; 17 per cent. of 240 males and 9 per cent. of 318 females. A similar sex incidence was noted by Davis and Weiss (1931); 20 per cent. of 272 males and 10 per cent. of 213 females. When the sexes are not differentiated an intermediate figure is found ; 12 per cent. of 348 patients with previously scarred valves in the combined series of Stone and Feil (1933), Frey (1936), and Epstein and Schwedel (1938).

Table XII shows that in males the incidence rose sharply at about 25, i.e.

TABLE XII

AGE AND SEX INCIDENCE OF ULCERATIVE ENDOCARDITIS ON SCARRED VALVES

Age Group	Males	Females
To 15	3	1
16 to 25	4	6
26 to 35	12	3
36 to 45	11	6
Over 45	12	13

the age when the fall occurs in the number with hearts previously normal: in females the incidence was relatively low except in people over 45. All but 5 of the 25 cases over 45 were septicæmic in type.

The numbers with each individual valve lesion are shown in Table XIII. In more than a quarter there was a spread of the ulcerative lesion to valves that had previously been undamaged. The frequency with which any chronic rheumatic valve lesion was affected by ulcerative endocarditis is also shown in this table. Ulcerative endocarditis affects about 36 per cent. of patients that have a pure chronic aortic lesion of rheumatic type, and this holds good when the cases are analysed according to sex or age ; it is the same in young women as in older men, though, of course, the absolute numbers of chronic aortic lesions are much higher in the male group. In chronic mitral or aortic-mitral lesions ulcerative endocarditis occurs in about 10 per cent. of cases, again without any significant sex or age differences. The low incidence of ulcerative endocarditis on the aortic in chronic aortic-mitral lesions, as compared with its higher incidence in chronic aortic lesions without fibrosis of the mitral, is of interest. White (1937) has suggested that there is a relationship between the degree of stenosis of the mitral and the tendency for ulcerative endocarditis to affect this valve, but we have not investigated this. In contrast to the other valves, patients with chronic tricuspid lesions show a very low susceptibility to ulcerative endocarditis, only about 4 per cent. ; the total incidence is actually less than that of ulcerative endocarditis on the tricuspid in patients with no chronic lesion of this valve. This may be because patients with chronic tricuspid lesions die earlier in life. Libman (1923) has shown that ulcerative endocarditis is relatively common on the tricuspid, as compared with subacute bacterial endocarditis. His total figures of 16 tricuspid involvements out of 156 cases of ulcerative and subacute bacterial endocarditis are in reasonable agreement with the present figures : 12 tricuspid involvements out of 169 cases of ulcerative or subacute bacterial endocarditis, with or without a previous chronic lesion.

TABLE XIII

ULCERATIVE ENDOCARDITIS ON SCARRED VALVES

Ulcerative Endocarditis	Chronic Valve Lesions					
	M	A-M	A-M-T	M-T	A	Others
None	270	174	47	29	37	3
M	**14**	4	1	1	0	0
A-M	5	**13**	0	1	8	0
A-M-T	2	0	0	0	1	0
M-T	1	0	0	0	0	0
A	1	6	0	0	**11**	0
Others	0	0	0	0	A-T	P-T (cong.)

V. PRIMARY AORTIC SCLEROSIS AND SYPHILIS

Lesions of the aortic valve due to syphilis or primary sclerosis are only important in the present study because they have to be differentiated from the

rheumatic lesions; only exceptionally does this provide any difficulty. The two conditions were nearly all found in patients over 45, though syphilitic cases were sometimes seen in the previous decade. After excluding all minor senile changes, the actual numbers were as follows—primary sclerosis: males 58, females 17; syphilis: males 82, females 14.

Small vegetations due to a superimposed acute endocarditis were present in four of the syphilitic and in eight of the sclerosis cases. This appears to be a chance complication, the incidence being roughly similar in the syphilitic patients and in those with otherwise normal hearts dying in the same age periods. The slightly higher incidence among the sclerosis cases is probably spurious, depending on the initial exclusion of many cases with minor thickening of the aortic, but without any acute vegetations. Gerhardt (1913) found a recurrent endocarditis in two out of eleven arteriosclerotic valves.

DISCUSSION

It is accepted pathologically that vegetations on a valve are frequently an indication of an acute valvulitis which may go on to scarring later. This applies particularly to acute rheumatism. On the other hand, it is impossible to say what might have occurred subsequently, if a patient with advanced carcinoma could have recovered after having developed a terminal endocarditis. There is, however, a large group, intermediate between acute rheumatism and terminal endocarditis, that includes not only simple endocarditis but also endocarditis recurring or spreading to other valves. Though, of course, all the patients in this intermediate group had died, most of them were suffering from diseases not necessarily fatal; it is in these that the subsequent fate of the valve is in doubt.

These hearts do not have the microscopic changes in the myocardium that characterize acute rheumatism, but this cannot be accepted as proof that scarring of the valve will not occur. The mere occurrence of the vegetations suggests co-existing acute valvulitis that could be the basis of subsequent fibrosis. If such scarring occurred on a previously normal valve, it would provide a reasonable explanation for a number of the cases of chronic valvular disease that originate in patients with no ascertainable history of acute rheumatism; if it developed from a recurrent endocarditis on a previously scarred valve, the mechanical lesion would be aggravated. There is also the complementary question of how often cases of acute valvulitis that leads to subsequent scarring of the valves may run their course without ever developing any vegetations on the valves. This is an important problem in children, as has been shown by de Vecchi (1931).

The significance of recurrent endocarditis is especially doubtful. Is it (*a*) a terminal condition, or (*b*) an occasional development in the presence of certain exciting factors, or (*c*) an intermittent process coming and going unsuspected for many years after the original heart lesion, without any particular causation apart from the continued and symptomless presence of the aetiological agent of rheumatism, or (*d*) a serious complication of chronic valvular lesions

that commonly causes death from the associated myocardial damage (Cowan and Ritchie, 1935) ?

A study of the present kind might have given some answer to these questions in view of the marked differences in the valves affected by acute or chronic lesions at different ages and in different sexes. There are, however, many difficulties in attempting any correlation. Account must be taken of four factors which may play a part in the distribution of the various types of valve lesions at different ages. First, the age at the onset, which is only known in a certain number. Secondly, the progress of the lesion ; if the case starts early, it seems more likely that it will progress on the affected valve and also spread to new valves than if it starts in later life ; this presumption is based on the age incidence of recurrent endocarditis. Thirdly, the age at which the valve lesion causes death, e.g. patients with a tricuspid lesion usually die earlier than patients who have not. Fourthly, a factor that has not been discussed, the severity of the individual valve lesion. It is, therefore, not possible to assume that the patients dying in any age group provide a representative sample of the cardiac population at that age. Nevertheless the group of children up to the age of 15 is probably subject to the least complications, and may be used for an attempt to find some correlation between acute or recurrent endocarditis on the one hand and chronic valve lesions on the other. The fundamental problem is how frequently chronic valve lesions are the sequel of acute endocarditis or are aggravated by a recurrent endocarditis. Such a recurrent endocarditis might be assumed for purposes of discussion to develop occasionally at intervals during the patient's life, as a result of temporary failure or intercurrent illness, and to have the same incidence on previously scarred valves or spreading to normal valves as is found post mortem.

Mitral and Aortic-Mitral Lesions in Childhood.—First the ratio of lesions affecting only the mitral to lesions affecting the aortic and mitral together. In girls up to 15, acute endocarditis without previous valve lesions involves both valves together just as frequently as the mitral alone. But during this age period in girls a chronic lesion affects the mitral alone three times as frequently as the aortic and mitral together. No satisfactory explanation for this preponderance of the pure chronic mitral lesion in girls can be given from a study of the acute endocarditis. On the other hand, in boys up to 15 the correlation is good ; the aortic and mitral are affected together very slightly more frequently than the mitral alone, both by simple endocarditis and by chronic lesions.

Mitral and Aortic-Mitral Lesions in Young Adults.—In girls up to 15 about one third of the patients with chronic mitral lesions have post mortem a spread of acute endocarditis to the aortic. Any fibrosis following these new vegetations ought to lead to an increase of chronic aortic-mitral lesions at the expense of chronic mitral lesions in the next decade. This is the case ; there are rather more chronic aortic-mitral lesions than mitral lesions post mortem in females between the ages of 16 and 25, in contrast to the findings in young girls. In boys up to 15 there are relatively few pure chronic mitral lesions and less than one fifth of these have spread to the aortic. Theoretically this should only cause

a slight increase in the ratio of chronic aortic-mitral to chronic mitral lesions in the next decade : this is again the case.

Tricuspid Lesions.—There is thus some suggestion that these spreading vegetations do lead to subsequent fibrosis in the case of the aortic. But when the tricuspid is under consideration this view completely fails to explain the facts : taking the figures for all ages ; (*a*) the incidence of simple acute endocarditis on this valve was identical in both sexes, 6 males and 6 females ; (*b*) in the presence of other chronic valve lesions, spread of acute vegetations to this valve was also the same in both sexes, 12 males and 12 females ; but (*c*) the incidence of chronic tricuspid lesions was about three times as high in females as in males, 60 females and 22 males.

In view of these difficulties even in young subjects, no attempt will be made here to explain the increasing incidence of chronic mitral lesions relative to other chronic valve lesions in older women.

Rheumatic Lesions

In Childhood.—The relation of the valve lesion to a history of rheumatism also presents difficulties. The preliminary consideration may be restricted to children up to 15 (Table XIV). In boys the proportion with acute endocarditis of any particular valve or valves and acute rheumatism in the few weeks before death is much the same as the proportion with a corresponding chronic lesion and acute rheumatism some years before. In girls this holds good for lesions of combined valves. But there is a striking difference with pure mitral lesions, where, though three-quarters of the chronic lesions have a history of rheumatism, as with other valves and in boys, only about one-third of the cases of acute endocarditis are related to rheumatism. The figures are small, but the difference seems significant.

TABLE XIV

Relationship of Rheumatism to Valve Lesions in Childhood

Sex	Valve	Cases of Acute Endocarditis	Acute Rheumatism at Death	Chronic Valve Lesions	History of Rheumatism
Males under 15 ..	M	5	3	8	5
	A-M	6	4	10	8
	A-M-T or M-T	4	4	3	2
	Total	15	11	21	15
Females under 15 ..	M	14	5	24	18
	A-M	12	9	6	5
	A-M-T or M-T	2	1	6	4
	Total	28	15	36	27

The other contrast is as follows. In acute endocarditis due to rheumatism in boys or in girls, the mitral is affected alone in about one-third of the cases and the other two-thirds show multiple valve lesions. In chronic valve lesions following rheumatism this also holds good in boys, the mitral being affected alone in about one-third. In girls, on the other hand, such lesions affect the mitral alone in two-thirds and only one-third are multiple valve lesions.

Subsequent Fate.—Theoretically, the longer the patient lives after the original valve lesion, the more he will be exposed to attacks of recurrent or spreading endocarditis ; and, if these lead to fibrosis, the greater the liability to multiple chronic valve lesions. But, when the cases of heart disease dating from acute rheumatism are studied with regard to the duration of life after the onset of the heart lesion, there is no evidence of any development of chronic lesions on fresh valves with the passage of time. The valve distribution shows the same sex differences, whether the rheumatism dates from early in life or later, and whatever the duration of life since the first attack of rheumatism. Table XV shows the

TABLE XV

CHRONIC VALVE LESIONS FOLLOWING RHEUMATISM

Sex	Chronic Valve Lesion	Acute Rheumatism before 15		Acute Rheumatism after 15	
		Death within 10 Years	Death over 10 Years later	Death within 10 Years	Death over 10 Years later
Males	M	5	4	3	4
	A-M	8	10	9	10
	A-M-T or M-T	2	3	0	1
	A	0	1	1	2
Females	M	18	15	12	12
	A-M	5	6	5	4
	A-M-T or M-T	4	2	3	7
	A	0	0	1	0

valve distribution of the chronic lesions of 157 cases in which the date of the first attack of rheumatism was known. The valve incidence of the chronic lesions that date from rheumatism is almost the same throughout life when each sex is considered separately. On the other hand, as has been shown earlier, there are quite marked age differences when the chronic lesions are considered as a whole, i.e. those following acute rheumatism and those without any such history. This raises the possibility that the cases following rheumatism may have a completely different valve distribution at various ages from those not following rheumatism. Taking all the chronic valve lesions of Table I the percentages in which a history of acute rheumatism was obtained are shown in Table XVI. The general fall with advancing age is probably partly due to a failure of memory by the patient, but this explanation will not account satisfactorily for the strikingly low figures in the case of pure mitral lesions in males over 15 years of age.

TABLE XVI

PERCENTAGE OF CHRONIC LESIONS WITH PREVIOUS RHEUMATISM

Age Group	Males				Females			
	M	A-M	A-M-T or M-T	A	M	A-M	AM-T- or M-T	A
To 15	63	80	66	0	75	83	66	0
16 to 35 ..	3	54	86	18	46	56	46	25
Over 35 ..	9	27	20	4	29	31	44	0

Consideration of the cases with a history of chorea does not show any striking differences from the findings for rheumatism in general, apart from a high sex incidence in females, most marked before the age of 25. There does not appear to be any association with any specific valve lesion. When all the chronic lesions are taken together, there was a history of chorea and of other acute rheumatism in 1 and 26 per cent. respectively of the males, and in 5 and 35 per cent. of the females. These figures are rather lower than those of Dunn and Hedley (1938), but they do not give details about the age and sex.

It will be seen that every attempt at correlation of chronic valve lesions with acute or recurrent endocarditis breaks down in some fundamental aspect, and that no satisfactory explanation can be offered for the sex and age differences in the various valve lesions. Nevertheless these differences appear to be important and to be of some definite significance.

SUMMARY

A statistical analysis was made of the pathological and clinical findings in 1057 necropsies on patients with acute or chronic valvular lesions, to ascertain the sex and age differences.

Chronic Rheumatic Valve Lesions.—There was a very high incidence of pure mitral lesions in young girls and of combined lesions affecting the tricuspid in women from 15 to 35. In males, combined aortic-mitral lesions were common throughout life, but tricuspid involvement was rare. The age of death in chronic mitral lesions was about the same as in chronic aortic-mitral lesions, but patients with chronic tricuspid lesions tended to die much earlier, nearly always as a result of congestive failure.

Recurrent Endocarditis.—Simple acute vegetations, developing on an old valve lesion or, less often, spreading to previously undamaged valves, were very common in childhood but progressively less frequent with advancing age. This recurrent endocarditis was rather more frequent in females ; it was very common in acute rheumatism or congestive failure, but was sometimes found with intercurrent diseases. The mitral and aortic were involved with about equal frequency, the tricuspid less commonly.

Simple Acute Endocarditis.—This was rare under 5 years of age. It was more common in older children, associated with acute rheumatism or chorea or

sometimes with acute infections or septic conditions. In adults the endocarditis was usually associated with infections or miscellaneous conditions ; in old age it was usually a terminal occurrence in carcinoma or cardiorenal disease. In acute rheumatism the lesion usually affected multiple valves : in non-rheumatic cases it usually affected the mitral alone, particularly in females, or the aortic alone, particularly in males ; combined lesions were uncommon.

Ulcerative and Subacute Endocarditis.—This was rather commoner in males than in females. When occurring on previously normal valves it was usually of septicæmic type in early life ; but in old age it was often only terminal, usually in association with carcinoma of the stomach or uræmia.

When developing on previously scarred valves it was commoner in middle life, particularly in males, and was usually of septicæmic type ; it was common on chronic aortic but rare on tricuspid lesions.

Primary Sclerosis and Syphilis.—This affected the aortic valve and was commoner in males than in females.

It is difficult to obtain any real correlation between the incidence of acute endocarditis, recurrent endocarditis, and the chronic valve lesions. Some of the acute lesions may lead to subsequent scarring of the valves, and some of the recurrent lesions to increase of the fibrosis in scarred valves or to the scarring of previously normal valves. The evidence on this matter is, however, inconclusive.

We wish to express our thanks to Professor Shaw Dunn, Professor Blacklock, and Dr. Montgomery for permission to study these autopsy reports.

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STENOSIS AT THE LOWER BULBAR ORIFICE OF THE INFUNDIBULUM

BY

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Received May 18, 1939

Stenosis at the lower bulbar orifice is not very rare, as Keith (1909) in the examination of two hundred and seventy abnormal hearts found it to be present in nineteen. We consider, however, that the associated abnormalities of this heart make the case worthy of publication.

The right ventricle is a composite chamber, formed partly by the transverse part of the primary ventricular loop and partly by the lower part of the bulbus cordis ; the bulbus lies between the common ventricle and the truncus arteriosus in the embryonic heart. The bulbus cordis persists in elasmobranchs and most of the reptiles as a chamber that remains separate from the ventricle, but in the mammalian heart part of the bulbus is incorporated in the right ventricle. Greil (1903) was the first to suggest that the part of the bulbus absorbed by the right ventricle is represented by the infundibulum (conus arteriosus) in the adult human heart. Keith (1924) considers that the function of the infundibulum in the mammalian heart is essentially akin to that of the bulbus cordis in the lower vertebrates, in which it persists as such ; that the bulbus acts as a guarding mechanism for the vascular network of the lungs against the raised blood pressure that occurs during increased cardiac activity; and that the musculature of the infundibulum passes into action later than that of the body of the right ventricle.

The component parts of the right ventricle in the human heart, however, may retain their individuality and only communicate with each other by a constricted orifice. This condition has been referred to by Keith as *stenosis at the lower bulbar orifice of the infundibulum*.

In such a heart the infundibulum itself is expanded above the orifice and forms a dilated, but relatively thin-walled chamber, which communicates freely with the pulmonary artery. The wall of the right ventricle below the orifice, i.e. the ventricle proper, is hypertrophied and is usually thicker than the wall of the left ventricle. The size of the lower bulbar orifice varies greatly in different specimens, and the duration of life tends to bear a direct relationship to the size of this orifice.

In the great majority of examples so far described there has been a deficiency

in the interventricular septum and in most of these the communication has been such as to provide a shunt between the two chambers. In four cases, recorded by Lafitte (1892), Jackson (1893), and Eakin and Abbott (1933), there was no interventricular foramen. Associated with this deficiency there is usually some degree of dextro-position of the aorta. This combination of defects is not surprising, as the incorporation of the bulbus cordis in the right ventricle normally takes place early in development before the completion of the septa and before the normal torsion of the arterial trunks. For the same reason a patent foramen ovale and a patent ductus arteriosus are sometimes found in association with these other changes.

Case Record

A. L., aged 38, was admitted to the Eastern General Hospital, Edinburgh.

History.—He had " heart trouble " of unknown nature when 17 years of age, from which he recovered well. He never had rheumatic fever, but suffered frequently from sore throats, the last being one week prior to the onset of his terminal illness. Throughout his life he had been unable to take violent exercise because it caused attacks of extreme breathlessness and cyanosis. No other illnesses were admitted.

One month before admission he began to notice weakness and marked tiredness on exertion and inability to walk more than a quarter of a mile without a rest. His feet, face, and tongue began to swell. He developed a cough with sputum, and for three weeks had suffered from diarrhœa. As the condition was progressing rapidly, he was sent to hospital.

Examination.—He was of medium size, with a sallow complexion, cyanosed lips and hands, and puffiness of the face. The fingers and toes exhibited clubbing. No purpuric spots were noted. There was œdema of the feet and legs and also a small lumbar pad.

The pulse was rapid (100 per minute), regular, and of good volume. Blood pressure, 150/100 mm. The vessel walls were not palpable. The apex beat was visible and diffuse ; on palpation it was forcible and was localized in the sixth interspace in the anterior axillary line. There was an apical diastolic thrill. On auscultation there was a harsh loud diastolic murmur of maximum intensity in the fourth interspace at the left border of the sternum, propagated in all directions. There was also a systolic murmur in the pulmonary area, propagated upwards for one inch towards the left.

Both bases were dull to percussion posteriorly and the respiratory sounds were diminished. The respiratory rate was 30. The sputum was slight in amount and consisted of a frothy mucus.

The abdomen was distended. The liver was not enlarged. Otherwise no abnormality was detected on clinical examination.

The urine contained much albumen and a faint trace of blood. Microscopically there were granular and epithelial casts and red blood cells. The hæmoglobin was 45 per cent.

Course.—The temperature swung between 97° and 101° during the first six days in hospital, but thereafter remained normal or subnormal. A blood culture was carried out twice during this pyrexial stage, but no growth was obtained. The œdema became worse, despite therapy. The spleen, which had not been palpable, enlarged progressively and became tender. At no time were any purpuric spots noted. The patient remained lethargic in his reactions for the first week, after which he became more torpid and eventually died in a coma two weeks after his admission.

Summary of Autopsy Findings.—The body was moderately developed There was slight but generalized œdema. The pericardial and peritoneal sacs contained several

ounces of clear serous fluid. Both pleural cavities were almost obliterated by dense fibrous adhesions.

The heart exhibited gross abnormalities which are given in detail below. The outstanding feature was the tremendous hypertrophy of the right ventricle.

Both lungs were congested and slightly œedmatous towards their bases ; no infarcts were detected.

The spleen weighed 750 g. No infarcts were present in the spleen or in the kidneys, both of which showed gross congestion.

No congenital abnormality was detected apart from that noted in the heart.

Anatomical Features of the Heart

The chief abnormalities present were : (*a*) stenosis of the infundibulum (conus arteriosus) at the lower bulbar orifice ; (*b*) hypertrophy of the right ventricle below the orifice ; (*c*) dilatation of the infundibulum ; (*d*) communication of the right ventricle with the anterior sinus of the aorta ; and (*e*) a small communication between the right and left ventricles.

The heart showed general enlargement (550 g. compared with an average of 330 g.), especially of the right auricle, which was markedly dilated, and of the right ventricle, which was more conspicuous than usual in the region of the infundibulum.

The walls of both right chambers were thickened. The wall of the right auricle had an average thickness of 4 mm., with prominent musculi pectinati ; the wall of the left auricle was 2 mm. thick. Beneath the anterior limb of the limbus of the fossa ovalis there was an oblique passage 10 mm. long just admitting a fine probe. This is the standard type of patent foramen ovale which is found in a large percentage of hearts (25–30 per cent.).

The right ventricle was subdivided by an obliquely placed septum into (*a*) the right ventricle proper and (*b*) the infundibulum (conus arteriosus) ; the only communication between these two subdivisions was a foramen in the septum which measured 7×5 mm. ; the edges of the foramen were white and fibrous. The general disposition of these parts of the chamber are shown in Fig. 1.

The wall of the ventricle proper was especially noteworthy on account of its unusual thickness. Near the lower margin of the heart it was 13 mm. thick, gradually increasing towards the base of the chamber to 24 mm. ; the thickness of the ventricular septum was, on an average, 15 mm., with a corresponding increase in the trabeculæ carneæ, moderator band, and papillary muscles. The tricuspid orifice in the fresh specimen was large enough to admit five fingers ; the chordæ tendineæ were much thicker than usual and near the cusp margins flattened out into membranous bands.

About 10 mm. in front of the left end of the base of the anterior cusp there was an opening, with a maximum diameter of 7 mm., that led into the aorta. The margins of this orifice were thin and membranous and in the fixed specimen had come together so as to occlude the passage. This connection between the right ventricle and the aorta indicates that there was some dextro-position of that vessel. The site of the upper opening of the orifice was especially note-

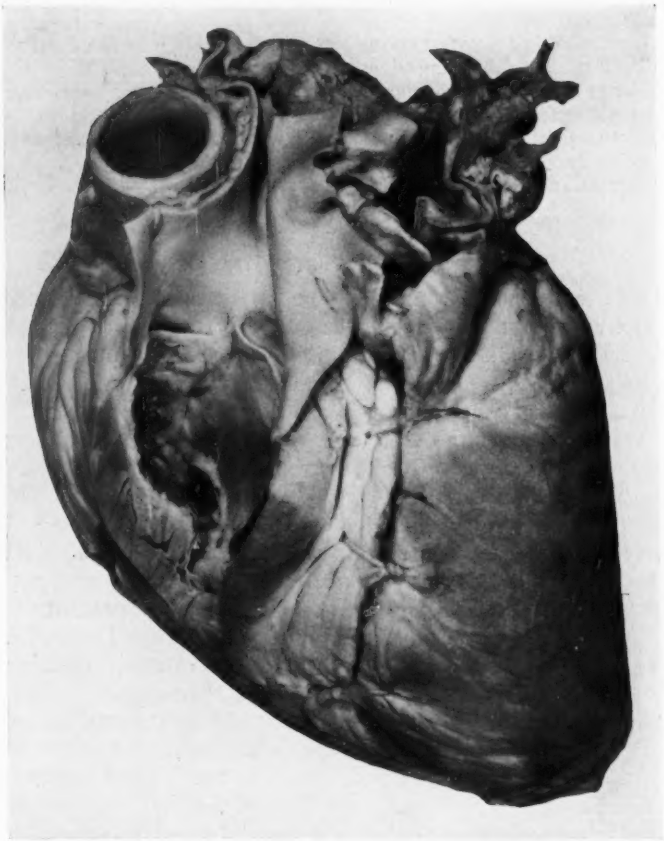

FIG. 1.—Anterior view of the heart. The interior of the infundibulum and the communication of this chamber with the body of the right ventricle is shown.

worthy in that it was actually into the anterior sinus—which was much enlarged —and was about 10 mm. below the origin of the right coronary artery.

Immediately behind the aortic opening, i.e. between it and the tricuspid valve, there was a small, slit-like orifice, 3 mm. long and just large enough to admit a fine probe, leading into the aortic vestibule. The opening of this communication into the right ventricle was so guarded by a flap-like fold of endocardium that, quite apart from its size, there could be little doubt that it had not functioned during life.

The infundibular part of the right ventricle (Fig. 2) was much enlarged. In general it had a slightly saccular form, with a maximum length of 31 mm. and a width of about 20 mm. The posterior wall of the chamber was smooth, but the anterior wall was roughened by several well-defined trabeculæ carneæ.

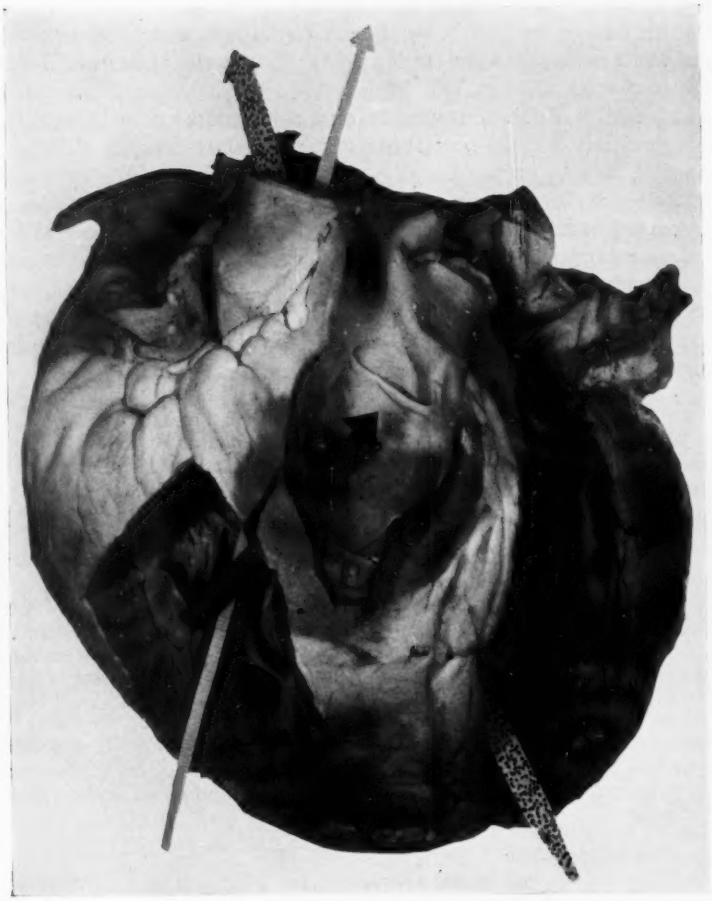

FIG. 2.—Anterior aspect of the heart. The interior of both the right and the left ventricles is shown and three arrows have been inserted to demonstrate the communications between the chambers. The *black* arrow has been passed from the body of the right ventricle into the infundibulum ; the *stippled* arrow passes from the left ventricle into the aorta ; and the *white* arrow from the right ventricle into the aorta.

The opening into the right ventricle proper was on the right wall of the chamber about 13 mm. above its most dependent part ; above, the chamber communicated freely with the pulmonary artery through the pulmonary valve. The cusps of the pulmonary valve had the normal anatomical arrangement and showed no stenosis. The wall of the chamber was not of equal thickness throughout, as in its lowest part it varied from 5 to 9 mm. and as it was traced upwards it gradually thinned and so imperceptibly merged with the wall of the pulmonary artery.

The wall of the left ventricle was relatively thin as compared with the right, as near the base of the heart it was 14 mm. (cf. 24 mm. in the right) and at the apex it was 7 mm. (cf. 13 mm. in the right). The aortic orifice was displaced slightly to the right.

The diameter of the aorta was 21 mm. as compared with 17 mm. in the pulmonary artery ; in the normal heart the pulmonary artery is slightly wider at its origin than the aorta.

Pathological Features.—In addition to these anatomical abnormalities there was endocarditis involving the opening between the right ventricle proper and the infundibular portion. Large fungating vegetations completely surrounded the orifice. No ulceration of the wall in this area could be detected, but the vegetations extended upwards from the orifice on to the wall of the conus arteriosus and involved the cusps of the pulmonary valve. They were growing through the orifice also and protruding into the right ventricle.

Microscopically.—The vegetations consisted of a fibrin thrombus with organization in its base ; this and the adjacent muscle was densely infiltrated with cells in which polymorphs were prominent. On the surface of the vegetations were clumps of cocci. On the conus side of the pulmonary valve there was a similar formation, but with a more cellular fibrosis and less cellular infiltration and fibrin clot. A large patch of hyalinized fibrous tissue in the wall of the conus had apparently arisen from the overlying endocarditic changes. The myocardial fibres underlying the endocarditis were somewhat hyalinized, and in the right ventricle showed considerable hypertrophy. There was some periarterial fibrous thickening, and thin strands of connective tissue could be seen extending out between the muscle bundles from the vessels. This feature was much more marked in the right ventricle than in the left. No Aschoff nodules were present, but there was some intimal thickening with scarring in a few of the smaller myocardial vessels. This was obviously of long standing, but was not specific enough to warrant a diagnosis of an old rheumatic lesion. The wall of the right auricle contained more fibrous and less elastic tissue than did that of the left. As compared with a normal heart, however, this variation was not so prominent as was the relative difference in the ventricles with the definite fibrosis in the wall of the right chamber.

Discussion

The case is a typical example of stenosis of the lower bulbar orifice of the infundibulum. Associated with this stenosis there was hypertrophy of the wall of the right ventricle, a minute opening in the ventricular septum, and a slight degree of dextro-position of the aorta.

The stenosis of the lower bulbar orifice in this case was essentially similar to that found in the cases of this anomaly reported previously. In these the measurements showed a wide variation, but the size in this specimen (7×5 mm.) was less than usual. The position of the orifice was not as usually described, however, as it was not in the most dependent part of the infundibulum, but about 13 mm. higher. The stenosed orifice was quite unguarded by any valvular mechanism and was probably responsible for the murmurs heard during life, though the vegetations around the orifice might have exaggerated them. The presence of bacterial endocarditis at the site of

the anomaly is in keeping with the view that such a lesion tends to occur in association with some pre-existing malformation.

The hypertrophy of the wall of the right ventricle proper was undoubtedly due to the small size of the pulmonary outlet. Associated with this hypertrophy there was a patchy fibrosis throughout the wall of this ventricle which was absent from the left ventricle. This fibrosis was, if anything, more pronounced in the subendocardial region of the myocardium, as had already been observed in a similar case reported by Eakin and Abbott (1933).

The opening in the ventricular septum was small and as it was guarded on the right side by a flap-like fold of endocardium it is felt there could not have been a veno-arterial shunt. Hence this case may be classed with these where the septum is complete. As already stated, stenosis of the lower bulbar orifice is generally found with a large defect in the ventricular septum, which allows free communication between the pulmonic and systemic circulations, so that these patients always have a slight cyanosis. The present case, however, only showed cyanosis during exertion, and it is justifiable to infer, therefore, that this must have been due to the stenosed bulbar orifice rather than to a veno-arterial shunt. This stenosis, while allowing a sufficient passage for normal activities, would interfere with the additional flow of blood that would usually pass to the lungs on exertion.

The aorta showed some degree of dextro-position and the manner of connection between the right ventricle and this vessel was of special interest. The opening was between the highest part of the right ventricle and the enlarged anterior aortic sinus, about 10 mm. below the origin of the right coronary artery. The orifice, which was 7 mm. in diameter, had a fibrous ring projecting into the sinus in the form of a cone. Probably, therefore, this had a valvular action and prevented the regurgitation of aortic blood in the right ventricle during diastole. This mode of communication, whereby the right ventricle opens into the aortic sinus, has never been recorded before so far as we are aware. The proximity of this ventriculo-aortic communication and the origin of the right coronary artery suggests that the former might have been responsible, by interfering with the blood supply, for the undue fibrosis present in the wall of the right ventricle.

Summary

A heart is described in which there was stenosis of the lower bulbar orifice of the infundibulum. This feature is not in itself rare, but the absence of a functional interventricular foramen makes the case unusual. The communication of the right ventricle with the anterior aortic sinus is a further feature of interest.

Despite the gross abnormalities that were present in the heart, the subject lived to the age of thirty-eight, when the occurrence of bacterial endocarditis was responsible for death.

We are indebted to Dr. R. B. McMillan, Superintendent of the Eastern General Hospital, Edinburgh, for permission to publish the clinical notes of this case. We should also like to express our thanks to Professors W. T. Ritchie and A. M. Drennan for their interest and helpful criticism.

The photographs were taken by Mr. T. C. Dodds of the Pathology Department, Edinburgh University.

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VOLUMETRIC RECONSTRUCTION OF THE HEART IN HEALTH AND IN DISEASE: A RADIOLOGICAL STUDY

BY

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Received May 12, 1939

Radiological study of the heart has now become a well-recognized and valuable procedure in the investigation of a cardiac patient ; certain changes in heart shape and size can only be demonstrated by this method. The rationale of fluoroscopy of the heart is that by rotating the patient into suitable positions each chamber may be made to form a border, so that a measure of its size and depth is obtained. The value and limitations of the radiological approach can be estimated only on the basis of a knowledge of the relative size and position of these chambers. To the student fresh from the dissecting and post-mortem rooms there is a bewildering difference between the configuration and relative anatomy of the heart chambers before and after removal of the organ from the body. To help to obviate this difficulty it was thought worth while to reconstruct, in permanent form, a series of life-size models of normal and diseased hearts, the study of which would enable the student to appreciate more readily the radiological changes of heart disease. This paper deals with the manner of their reconstruction, with a description of each model. In addition, a few remarks about some more or less controversial points in the gross anatomy of the heart and great vessels are included.

The Method of Reconstruction

The first step in the procedure was devised by Palmieri (1921) and, although in itself it has not any important clinical application, it provides us with a clay replica of the heart that forms the basis of our final reconstruction ; in Fig. 1 is illustrated the principle of the method.

First Stage.—This is entirely a fluoroscopic procedure, the object being to obtain a series of tracings of the cardiovascular silhouette in different degrees of rotation of the patient. The patient is placed on a revolving stool, the vertical axis of which passes approximately through the centre of the heart. The X-ray tube is at the ordinary distance from the patient. The distances of the tube from the heart axis and from the fluoroscopic screen are measured and recorded ; these are kept constant in all examinations. By central (not

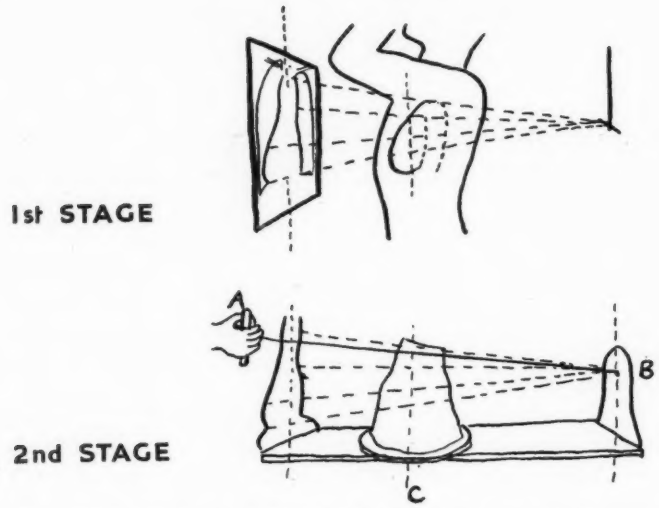

FIG. 1.—Diagram illustrating Palmieri's method of radiological volumetric reconstruction of the heart. *First stage :* by fluoroscopic examination in different degrees of rotation of the patient tracings are obtained of the cardiovascular silhouette by central projection. *Second stage :* the tracings are cut out in cardboard and, with the apparatus shown, a length of wire AB is moved along the edge of the cardboard section and pieces from a block of plastic material C are cut off. With each cardboard section the block is rotated into the corresponding position. When the manœuvre is completed a replica of the heart is obtained. (Modified from Palmieri (1921).)

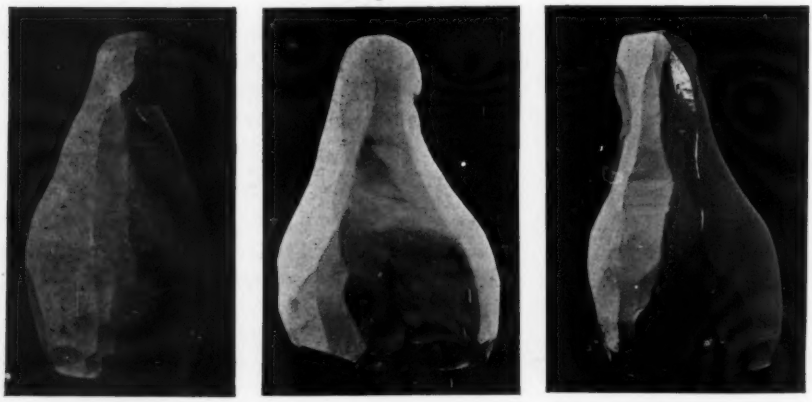

FIG. 2.—Clay replica of a normal heart obtained by Palmieri's method. Anterior, left and right oblique views.

orthodiagraphic) projection a tracing of the heart and great vessels is made on the screen in the anterior position. The tracing is made with lipstick so that a sheet of paper pressed against the screen will record the outline obtained.

L.O. ANT. R.O.

FIG. 3.—Clay replica of a normal vertical heart, with low diaphragm. Anterior, left and right oblique views.

The markings on the screen are then erased, the patient rotated through 30 degrees and a second tracing made. Of course, the heart shadow must be centred before each tracing. The use of lipstick renders it possible rapidly

L.O. R. O. ANT.

FIG. 4.—Clay replica of a normal transverse heart, with high diaphragm. Anterior, left and right oblique views.

to transfer the tracing from screen to paper in the dark, thus avoiding the necessity of interrupting the pupillary accommodation. Twelve tracings are made of the heart outline in different projections by rotating the patient through 360 degrees. The angle at which each drawing is made is recorded. Certain

L.O. ANT. R.O.

FIG. 5.—Clay replica of heart in case of mitral stenosis. Prominence of left pulmonary artery and conus in anterior view ; bulging of left auricle in right and left oblique views ; enlargement of right side of heart. Anterior, left and right oblique views.

L.O. ANT. R.O.

FIG. 6.—Clay replica of heart in case of free aortic regurgitation, showing prominent aortic knob and enlargement of left ventricle. Anterior, left and right oblique views.

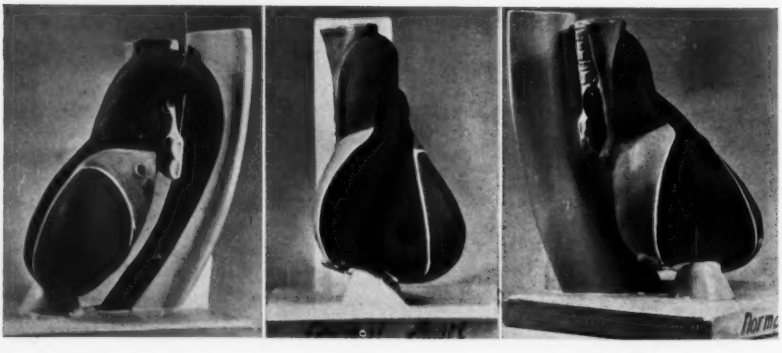

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FIG. 7.—*Model* 1. *Average normal heart.* A modification of Taipale's model (1934). The correct juxtaposition of œsophagus and arch of the aorta is shown ; the convexity of the right heart border has been reduced by narrowing the width of the base of the right ventricle ; the apex of the heart is formed entirely by the left ventricle ; the left auricular salient is reduced.

difficulties arise which make it impossible to obtain a *complete* outline in every view. The diaphragmatic surface of the right ventricle is not visualized in the anterior view ; in young people the arch of the aorta and the posterior border of the left auricle are difficult to make out in the left lateral and oblique views ; in the postero-anterior view, the upper segment of the left heart border is partly hidden. In spite of these limitations, prolonged accommodation of the eyes in the dark room and repeated examinations made it possible to obtain such tracings in a number of patients with the commoner forms of heart disease.

Second Stage.—The paper tracings are cut out in stiff cardboard and, with the apparatus shown in Fig. 1, a replica of the heart is cut off from a block of plastic material. The apparatus consists of a plank of wood equal in length to the measured distance between the X-ray tube and the screen. At C, a point corresponding to the vertical axis of the revolving stool (and of the

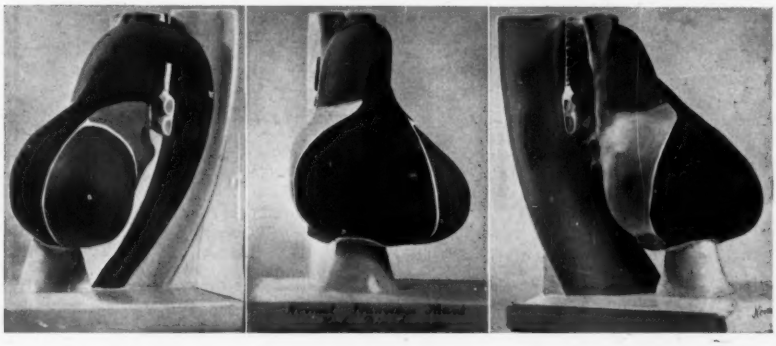

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FIG. 8.—*Model* 2. *Transverse type of heart*. The axis is approximately at right-angles to the great vessels. The level of the cardio-aortic junction is raised and the vascular pedicle is shortened. The transverse diameters of heart and vascular pedicle are increased. In the left oblique view the arch of the aorta is curved on a large radius. The retrocardiac space is increased.

patient's heart), a hole is bored and over this is placed a disc of wood marked off in degrees. A block of soft artist's modelling clay is centred about this axis on the wooden disc. At one end is a wooden upright to which is fastened a length of piano wire AB ; the point B corresponds to the position of the centre of the X-ray tube. At the other end are placed two grooved uprights which serve to hold the cardboard sections in position. Thus the screen is replaced by the cardboard sections, the body of the patient by a block of plastic material, and the tangential X-ray beam by the length of piano wire.

The first cardboard section, showing the cardiovascular silhouette in the anterior view, is placed in position and the wire moved along the edge ; and in so doing it cuts off a part of the clay. The latter is then rotated through 30 degrees when the corresponding section is inserted and the manœuvre repeated. When each heart outline has been cut and the clay has been rotated through 360 degrees, the replica of the heart is complete. It is a fairly accurate

reconstruction of the body of the heart and part of the aortic arch. Such clay models then serve as the foundation for our final reconstruction. Figs. 2, 3, 4, 5, and 6 illustrate plaster casts of such clay replicas.

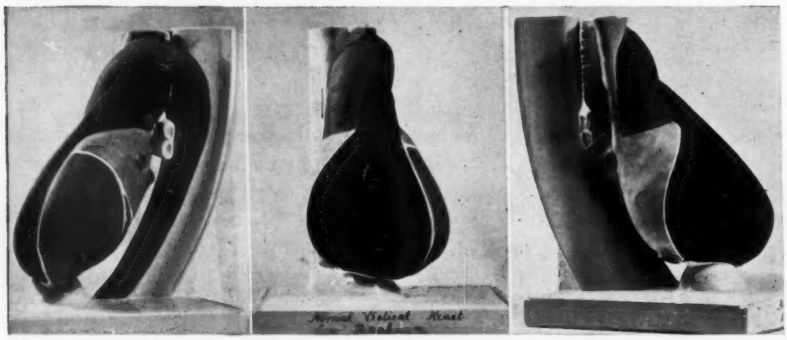

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FIG. 9.—*Model* 3. *Vertical type of heart.* The transverse diameters of the heart and the vascular pedicle are both reduced. The diaphragm is low in position and the convexity of all contours in all views is only slightly prominent. The right ventricle may participate to a small degree in the right heart border. The arch of the aorta appears short in the left anterior oblique view and is curved on a small radius. Both the dorsal and ventral cardiac contours are rather flat. The retrocardiac space is comparatively small.

Third Stage.—Palmieri's reconstruction did not proceed beyond the second stage. However, Taipale (1934) has constructed a porcelain model of a normal

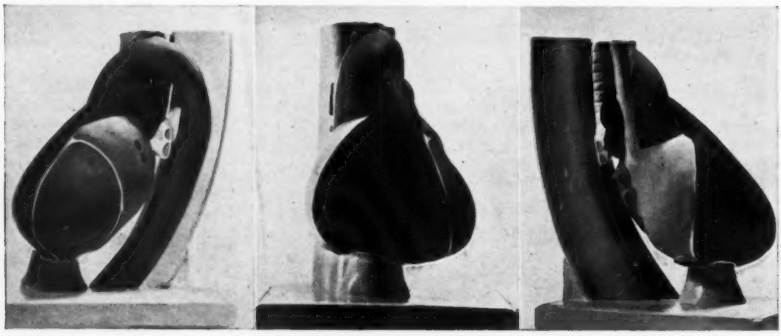

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FIG. 10.—*Model* 4. *Moderate mitral stenosis.* Anterior view shows straightening of left heart border, due to prominence of pulmonary artery and conus and left auricle. Moderate dilatation of the pulmonary artery. Left anterior oblique view shows enlargement of the left auricle. The retrocardiac space is diminished especially in its upper and middle thirds. There is no elevation of the left main bronchus.

heart which was based on many fluoroscopic examinations. Although not free from error, it is undoubtedly one of the most useful models yet made, especially from the radiological point of view. For this reason, and because

of the high degree of artistic finish of the model, it was decided to fashion our own abnormal models on similar lines, but owing to the prohibitive cost of porcelain manufacture it was arranged to cast our model in plaster.

A wooden armature was constructed, consisting of a base, 7½ inches square and 1 inch in thickness, with an upright 8½ inches in height carved to represent the vertebral column. The clay replica was placed in position in front of the column, supported on a wooden pedestal and transfixed in its vertical axis by a screw driven through the base. With this as a foundation, the position of the heart chambers, interventricular, and auriculo-ventricular grooves were indicated and the great vessels, œsophagus, and trachea built up according to their position as outlined at fluoroscopy. Deviations of the œsophagus were

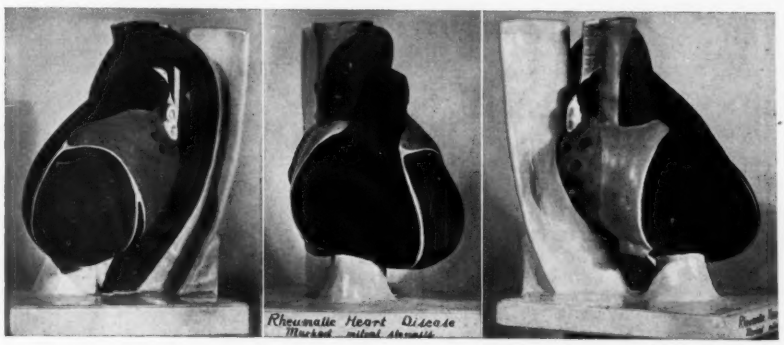

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FIG. 11.—*Model 5. Marked mitral stenosis.* Left auricular enlargement causes a convexity on the left heart border below the dilated pulmonary artery and conus. In the anterior view the left auricle can be seen on the *right* border of the heart, projecting above and behind the right auricle. Enlargement of the left auricle has obliterated the upper two-thirds of the retrocardiac space and has elevated the angle of bifurcation of the trachea and left bronchus. The œsophagus is displaced to the right by the enlarged left auricle and takes a wide sweep before it crosses to the left side of the descending aorta just above the diaphragm. In the lateral view the prominent pulmonary artery and conus make the anterior heart border convex. There is moderate dilatation of the right ventricle and right auricle.

detected by a barium swallow, and the position of the trachea recorded as accurately as possible. It was not considered necessary to outline the tracheal bifurcation with lipiodol. The intraventricular notch could not be visualized in each case and the position of the auriculo-ventricular grooves had to be obtained from observations on post-mortem controls. The position of the diaphragm was indicated by raising or lowering the pedestal upon which the heart rested. Except when the width of the descending aorta could be readily measured, an average was struck and maintained in all models in which the aorta was normal.

On completing such a model in clay, it was cast in plaster, shellacked, coloured, and inscribed. Twelve such models have been completed and they are illustrated in Figs. 7–18 of this paper with a description of each, with photographs in the anterior, left oblique, and right oblique views.

SOME ANATOMICAL COMMENTS OF RADIOLOGICAL INTEREST

One error in Taipale's model of the normal heart needed correction ; it concerned the position of the œsophagus in its relationship to the arch of the aorta. Taipale failed to show that the œsophagus normally receives an

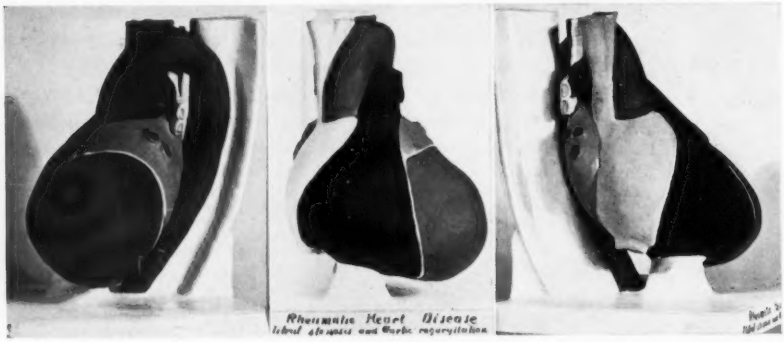

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FIG. 12.—*Model 6. Mitral stenosis and aortic regurgitation.* Besides the features of mitral stenosis, as described in Model 5, there is also marked left ventricular enlargement, due to aortic incompetence. In the left oblique view the lower third of the retrocardiac space is largely obliterated by the enlarged left ventricle.

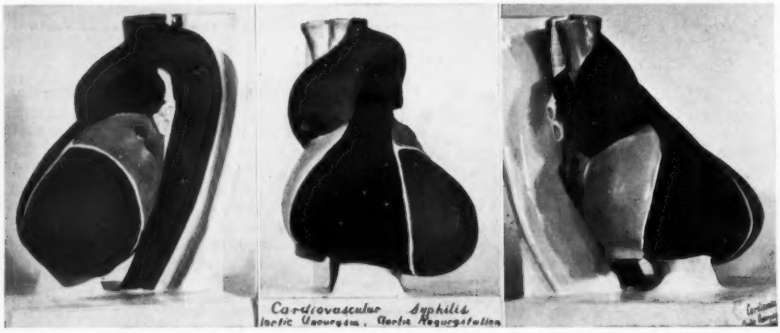

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FIG. 13.—*Model 7. Aneurysm of the ascending limb of the aortic arch, with aortic incompetence.* The left ventricle is enlarged. The aneurysm projects to the right beyond the right margin of the superior vena cava, which is displaced posteriorly and to the right. The aortic knob is prominent, presenting a marked convexity on the upper left border of the vascular pedicle. The trachea and œsophagus are displaced posteriorly and the latter is compressed against the vertebral column.

impression, roughly 3 cm. in length, from the right wall of the aortic arch just as that vessel begins to descend (Evans, 1936). In his model there is a distinct gap at this level due to the displacement of the œsophagus to the right.

Somewhat more debatable but no less important features are the degree of prominence of the right heart border and the width of the base of the right

ventricle. In the anterior view the right border, correctly shown to be entirely composed of the right auricle, is too prominent, while the width of the base of the right ventricle is exaggerated. The latter measurement places the interventricular groove and notch rather to the left of the normal, so that the heart apex comes to be formed by both right and left ventricles. This is undoubtedly not true in the normal heart, in which the apex is formed solely of left ventricle. For these reasons we have modified Taipale's model and constructed what we regard as an average normal heart (Fig. 7, Model 1).

The Superior Vena Cava.—Studies of the normal heart post-mortem, after radio-opaque injection, and observations upon the wax-injected heart in situ indicate that the true position of the superior vena cava in relation to the ascending limb of the aortic arch is not properly appreciated. Illustrations of the heart in most anatomical texts and the majority of papier-mâché composition

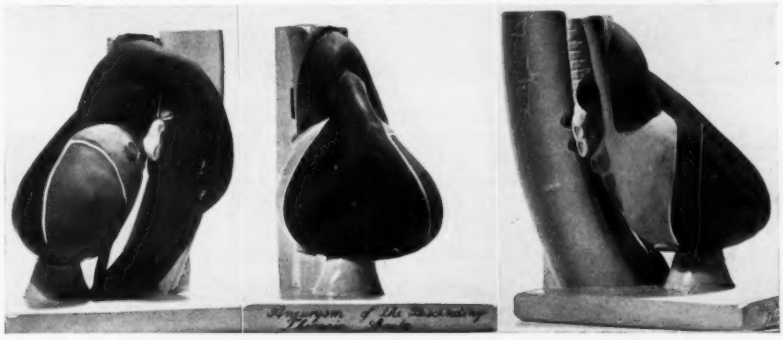

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FIG. 14.—*Model* 8. *Aneurysm of the descending thoracic aorta.* The heart size and configuration are normal. In the anterior view, the dilated descending aorta is seen well to the left, disappearing behind the heart at the level of the junction of the left auricle and left ventricle. In the left oblique view, the aneurysm, fusiform in type, is seen projecting beyond the left margin of the vertebral column, eroding the latter and adherent anteriorly to the left bronchus, which is stenosed and deformed. In the right oblique view erosion of the anterior aspect of two adjacent vertebræ is seen.

models in anatomical museums portray the superior vena cava as lying well to the right and only slightly posterior to the root of the aorta. This is quite inaccurate. The superior vena cava lies almost wholly posterior to the root of the aorta and rarely projects more than half a centimetre beyond the right aortic border at this level. Thus in a teleradiogram or orthodiagram the right border of the vascular pedicle in its lower third indicates the position of the right border of the ascending aorta. Mainly concerned with the dried, preserved corpse, the anatomist has for decades depicted these two vessels lying in practically the same plane.

The Right Ventricle.—The right border formed by the right ventricle has likewise been inaccurately depicted. If a glass plate is placed over the opened thorax of the corpse and a tracing is made of the heart outline, it will readily be seen that, when it is compared with an orthodiagraphic tracing of the

same patient taken during life, the right heart border is formed entirely by the right auricle. In the anterior view the right ventricle takes no part in the formation of the lateral heart borders. One exception might be mentioned, namely, the " drop " heart found in tall, spare individuals with a low diaphragm,

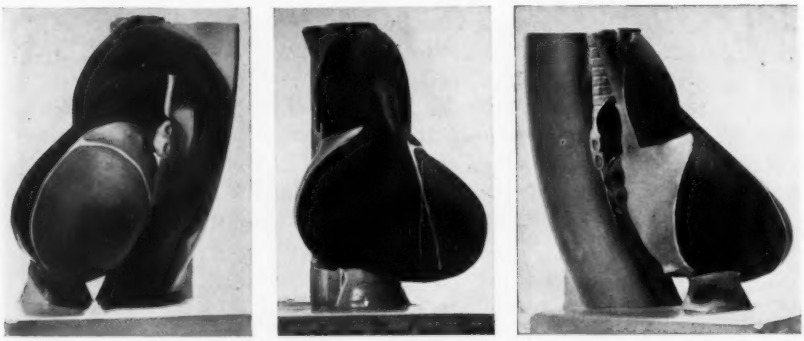

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FIG. 15.—*Model* 9. *Hypertensive heart and tortuous arteriosclerotic aorta.* Characteristic enlargement of the left ventricle and also widening and tortuosity of the whole aorta. In the anterior view, the ascending limb projects to right of the superior vena cava, while the arch runs obliquely backwards to the left, instead of almost directly backwards. The aortic knob is accentuated and the whole arch takes a wide curve, due to lengthening of the aorta. The descending aorta projects posteriorly and to the left and its lower third is kinked as it passes forward to descend through the diaphragm.

L.O. ANT R.O.

FIG. 16.—*Model* 10. *Chronic cor pulmonale.* Enlargement of the right ventricle and pulmonary arterial trunk. In the anterior view the pulmonary artery and conus are prominent and form a marked convexity on the left heart border. In the lateral view the anterior border of the heart presents a marked prominence in the region of the conus due to enlargement of the outflow tract of the right ventricle.

in whom the right ventricle may take part in forming a very small segment of the right heart border near the entrance of the inferior vena cava. This point is of some importance as it means that slight enlargement of the right ventricle is not detected in the anterior view ; the outflow tract, which is the first to show signs of enlargement, can only be viewed in the oblique or lateral positions.

The Left Auricle.—Whether the left auricle takes any part in the formation of the left heart border has been the subject of much debate ; modern opinion is that it does not. Indisputable evidence on this point is difficult to obtain, but the impression one has obtained during the course of this study is that,

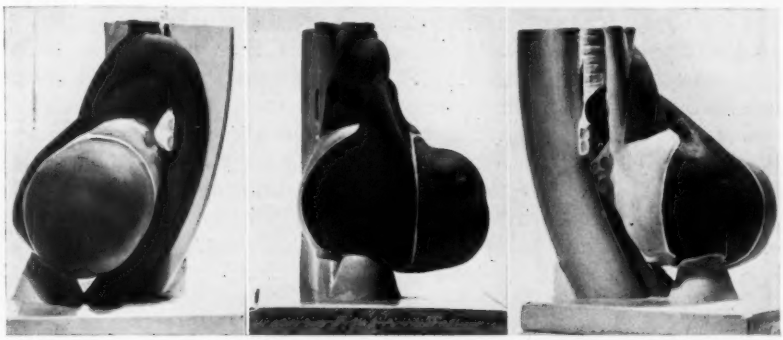

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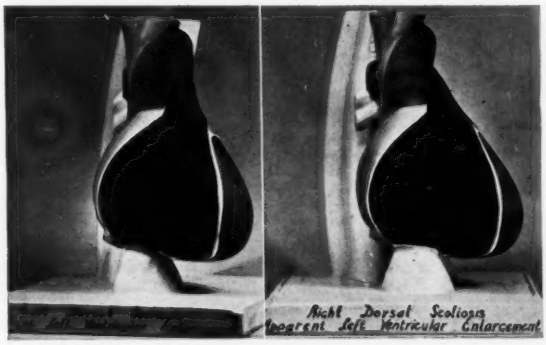
FIG. 17.—*Model* 11. *Myocardial infarction and aneurysm of the left ventricle.* Boot-shaped appearance of the heart in the anterior view, due to bulging of the left ventricle near the apex. The ventricle projects to the left and posteriorly, is rounded in shape and presents a shallow concavity on its left lateral margin. In the right oblique view there is characteristic " ledging " as the aneurysmal sac bulges forward from the main cardiac mass. In the left oblique view the retrocardiac space is reduced in its lower third.



SLIGHT ROTATION. ANT.

FIG. 18.—*Model* 12. *Right dorsal scoliosis with apparent left-sided enlargement of the heart.* The moderate, adolescent type of scoliosis gives the impression of left-sided cardiac enlargement with prominence of the aortic knob. When rotated slightly to the right, however, the scoliotic effect is counterbalanced and the heart appears normal. (Parkinson, 1936.)

certainly in some cases, a small segment between the pulmonary artery and left ventricle is formed by the triangular auricular appendage and adjacent wall of the left auricle. In our modification of Taipale's model of a normal heart we have reduced the auricular salient from 3 cm. to 1·5 cm. A longer arc

is only likely to occur in the " vertical " heart with a long, almost perpendicular, pulmonary artery.

The Pulmonary Arc.—Reference should be made, in passing, to the misconception that prevails in some quarters that the second curve on the left heart border in the teleradiogram or orthodiagram is formed by the conus of the right ventricle. It is sometimes loosely referred to as the " pulmonary conus." The conus of the right ventricle, however, lies well within the limits of the heart shadow in the anterior view. The pulmonary arc is formed by the trunk and left main branch of the pulmonary artery. An opportunity of making direct observations on this question has recently been afforded R. E. Gross (1939) during his operation for ligation of the patent ductus arteriosus. In several cases he states that he has observed the pulmonary arc to be formed mainly by the left pulmonary artery ; clips placed on this vessel at operation delimited the pulmonary arc in a subsequent teleradiogram.

Summary

A technique has been described whereby life-sized models of the heart in health and disease have been reconstructed. A description of each model in a series of twelve has been furnished, together with photographs of each in the anterior, left oblique, and right oblique views.

With the co-operation of the American Heart Association it has been possible to arrange for their distribution to those interested, in the hope that they will prove useful in the teaching of cardiology and of fluoroscopy of the heart. Enquiries should be addressed to the American Heart Association, Radio City, 50 West 50th Street, New York City, U.S.A.

I wish to tender my acknowledgments and thanks to Dr. Paul D. White for much helpful guidance and criticism during the course of this study, undertaken while holding a Commonwealth Fund Fellowship in the Department of Cardiology, Massachusetts General Hospital, Boston.

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THE KINKED CAROTID ARTERY THAT SIMULATES ANEURYSM

BY

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Received August 21, 1939

During the last fifteen years we have observed a number of patients in whom there was a pulsating vascular swelling at the right side of the root of the neck which at first sight suggested a carotid or innominate aneurysm. Subsequent investigation enabled aneurysm to be excluded and proved the vascular swelling to be a tortuosity or kinking near the origin of the right carotid. Often the pulsating tumour was the main or the sole complaint, and sometimes surgical treatment for aneurysm had been contemplated.

HISTORICAL

Coulson (1852) described a woman, aged 82, " who for some years before her death had a pulsating tumour, of the size of an orange, just above the right clavicle, in the situation of the carotid. The swelling had not of late increased in size and caused no inconvenience ; the woman died from natural decay. The vessels arising from the aorta were elongated and considerably dilated ; and the tumour, which was considered before death to be aneurysmal, consisted of a reduplication of the right common carotid. The interior of the vessels was highly vascular and there was considerable atheromatous deposit."

Hulke (1893) described a case like that of Coulson's, but without necropsy. She had " a conspicuous pulsating swelling which projected the sterno-mastoid muscle " and was thought to be an aneurysm of the common carotid artery. He concluded that the swelling was formed by a long loop of the carotid artery, comparable with the tortuosities found in more superficial arteries.

Douglas Powell (1909) reported upon a female, aged 78, with a pulsating tumour presenting the character of an aneurysm about the size of a walnut. It was defined as a widened, bent, and slightly twisted carotid artery. It proved to be a high division of the innominate artery, with a twisted kinked [*sic*] condition of the carotid, the walls of which were atheromatous and partially calcareous. At necropsy, " The right carotid was tortuous and considerably displaced. It was twisted to the right, forming a marked curve, about one-third of a circle ; it also showed antero-posterior deviation as well. The right

subclavian was likewise tortuous and directed at first somewhat backward, so that the innominate appeared to be slightly twisted. The left carotid and subclavian were normal in course. The aorta, right carotid, and subclavian all showed marked signs of atheroma" (Fig. 1). In the same paper he also

FIG. 1.—Sir R. Douglas Powell's specimen of kinked carotid, showing high bifurcation of the innominate. (*Middlesex Hospital Journal*, **13**, 2, 1909.)

referred to a woman, aged 60, whom he had seen fifteen years previously. She had a "degenerated, bent, and throbbing carotid artery which had simulated aneurysm, but it was clear on careful manipulation that the condition was a bent artery with locomotor impulse."

Stadler and Albracht (1911) attributed a similar swelling at the root of the neck to sclerosis and dilatation of the innominate artery. Hirschfelder (1918), in describing a case where a tortuous subclavian artery presenting its convexity in the supra-clavicular fossa had previously been diagnosed as aneurysm, noted the simulation of aneurysm by a tortuous carotid or subclavian artery. Balfour (1898), in a chapter on the simulation of aortic aneurysm by malposition of the aorta due to rickets, gave details of a woman, aged 46, who had severe dorsal scoliosis with convexity to the right and some kyphosis. She had noticed a throbbing swelling in her neck "as large as a hen's egg." In the lower part of the neck, just over the suprasternal notch, a pulsating tumour was felt crossing the trachea and dipping beneath the right sterno-mastoid muscle. At necropsy the heart was tilted up and the great vessels were displaced. The ascending aorta passed outwards to the right more than usual and continued into the transverse part at a somewhat acute angle. The innominate artery

was two inches long and twice its usual diameter. It came off from the aorta farther to the left than usual, coming to the surface at the left sterno-clavicular articulation and then crossing the trachea in the lower part of the neck to the edge of the right sterno-mastoid muscle, beneath which it dipped and divided.

Brown and Rowntree (1925) drew wider attention to the condition by publishing a series of five cases, all women, with pronounced pulsation of the lower right cervical region beneath the sterno-mastoid muscle. All their patients had hypertension. They attributed the condition to kinking or buckling of the right common carotid artery caused by the adjustment of a lengthened carotid artery to the decreased distance from the aorta (which is elevated) to the skull. They concluded that this kinking depends upon hypertension and does not result from arteriosclerosis alone.

Beardwood (1931) described two cases of hypertension, one a male, with this type of pulsation. He attributed the kinking to the fact that the carotid is fixed to some extent at its distal end, and that the aorta in enlarging pushes up the innominate artery almost out of the chest cavity. Additional examples, all women with hypertension, have been reported by O'Malley (1924), Eastwood (1927), Stolkind (1934), and Holst (1934). Recently Torrens and Horton (1938), in describing two more cases, state that none has yet been reported without hypertension. White (1937) refers to this pulsation, which he attributes to two factors—firstly vascular dilatation and secondly elevation of the great vessels by cardiac enlargement and a high diaphragm.

A somewhat similar condition due to elevation of the subclavian artery, especially the right, was described by Faure (1874) as a sign diagnostic of a dilated aorta. He described six cases, three with necropsies, in which there was elevation of the innominate artery with tortuosity of the subclavian. Barié (1912) also refers to this sign. The abnormal pulsation is at the root of the neck on the right side, but external to the sterno-mastoid. Norris and Landis (1933) also attribute " marked pulsation just above and to the right of the sterno-clavicular joint " to lifting up of the subclavian artery as the result of dynamic or passive dilatation of the arch of the aorta.

Clinical Features

The typical patient is a woman, middle-aged or elderly, often stout, and affected by kyphosis and scoliosis. A pulsating swelling is seen and felt behind the sternal head of the right sterno-mastoid, often extending beyond the inner or the outer border or even both borders of that muscle. A drawing of the neck showing a common position of the swelling is shown in Fig. 2. The pulsation is expansile and forcible, and the excursion to the right may attain 1–2 cm. The swelling is either rounded or ovoid, with its long diameter more or less vertical. In favourable cases, careful palpation with the finger-tips shows that it consists of a vascular loop—a bend or kink in the course of the right carotid artery. The size of the swelling is little affected by posture, though it may be a little more noticeable when the patient lies down. It varies in size

from time to time and may increase with rise of blood pressure or with tachycardia. There are no local pressure symptoms beyond the throbbing.

Our series comprises forty cases of this condition of kinked carotid, all being women with hypertension or arteriosclerosis or both. In addition, we

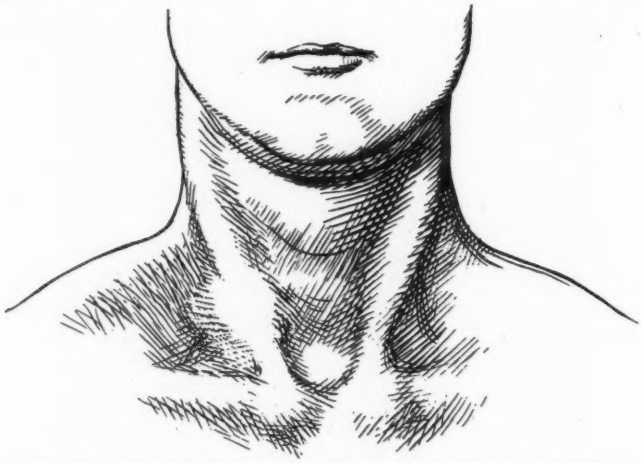

FIG. 2.—Drawing of neck to show a common position of the swelling due to kinked carotid.

have occasionally observed an almost identical vascular swelling in association with aortic incompetence and also with coarctation of the aorta ; these are separately considered.

Group I. With Hypertension or Arteriosclerosis (40 *cases*)

All were women ; the youngest was aged 41 and the oldest 79, the average being 59 years. The build and appearance were noted in 26 cases, and though 16 of these were obese, 6 were thin. Scoliosis, with the main thoracic convexity to the right and combined with some degree of kyphosis, was almost the rule. Ten of these 40 sought advice solely because of the local pulsation and swelling ; 13 mentioned it in addition to other symptoms.

Hypertension was present in 30 cases (75 per cent.), the blood pressure exceeding 160/95 mm., and in 24 of them the systolic pressure was above 200 mm. In 10 (25 per cent.) the blood pressure was never found raised. Thickening and tortuosity of the radial and brachial arteries were noted in half the cases. None showed evidence of syphilis and in 22 with a recorded Wassermann reaction there was only one positive finding.

There appears to be only one male with kinked carotid on record (Beardwood, 1931) and we also have seen one but have no notes of it. In two of our patients a similar (though less prominent) pulsatile swelling to that on the right was seen in the same position on the left side.

The cardiographic feature was left axis deviation, as would be expected

from the frequency of associated hypertension and a raised diaphragm. Bundle branch block was noted twice and auricular fibrillation twice.

The *X-ray* appearance of the aorta was notable. In 32 cases it was lengthened and uncoiled ; in the remaining 8, 2 were not X-rayed, 4 were inadequately reported, and 2 only showed no abnormality. In 16 the summit of the aorta reached the clavicle and in 2 it extended above the upper border of the clavicle. The heart was commonly enlarged, especially to the left, as expected with hypertension. In a few cases a shadow encroached upon the inner side of the apex of the right lung (Figs. 3 and 4), when it coincided with the area of the pulsating swelling as felt during radioscopy.

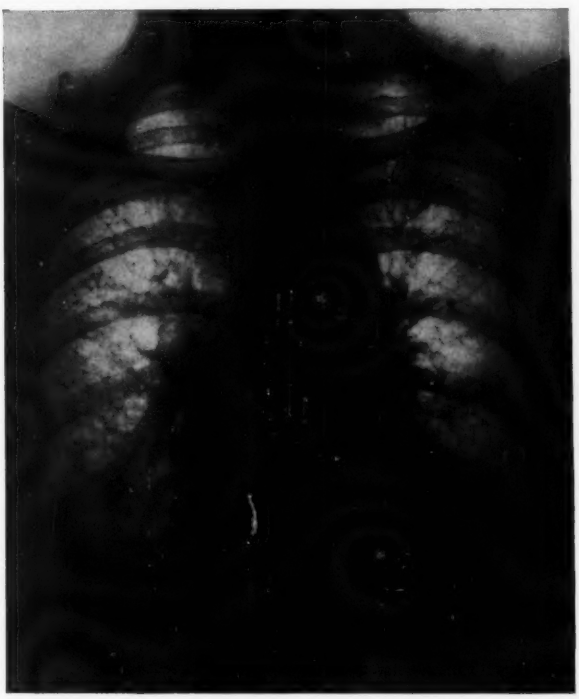

FIG. 3.—Radiograph showing an abnormal shadow at the apex of the right lung due to a kinked carotid. (Case 2 in Appendix.)

The prognosis depends on the cardiovascular disease and is not affected by the presence of a kinked carotid. One patient, first seen in 1923, was alive and well when re-examined fifteen years later at the age of 78. Two others have been under observation for eight and five years respectively, and in several others the swelling had been noted for as long as five to twenty-five years ; even over such long periods there seemed to be little or no increase in the size of the swelling.

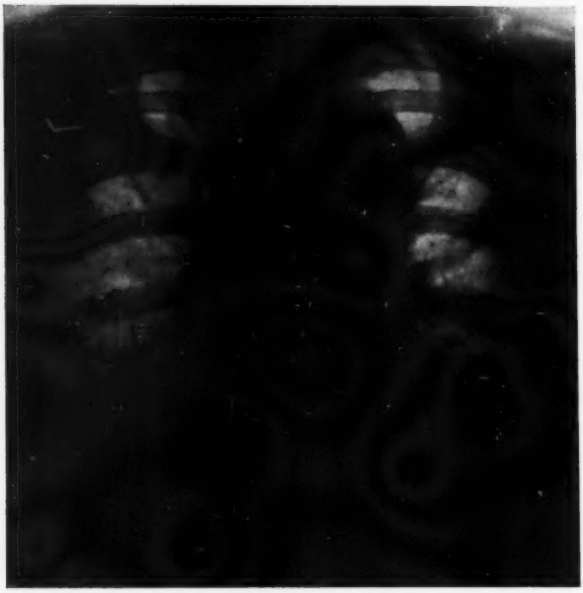

FIG. 4.—Radiograph showing a high aortic arch and an abnormal shadow at the apex of the right lung due to a kinked carotid. (Case 4 in Appendix.)

Group II. With Aortic Incompetence (4 *cases*)

Corrigan (1832) in his original paper *On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves* stated : " If the arch of the aorta and arteria innominata approach more nearly than usual to the notch of the sternum, the visible pulsation at the root of the neck becomes so prominent as to lead to a supposition that there is aneurysm, and even of considerable size at this part." And again : " So strong were the pulsations for years in the region of the arterio-innominate that until the examination after death there was never even a doubt expressed that the case was not aneurysm."

Hare (1886) reported a girl, aged 17, with rheumatic aortic incompetence " and an egg-shaped protrusion in the suprasternal notch, very expansile and bulging at each systole of the heart " ; he considered it to be a small fusiform aneurysm, combined with general dilatation of the aorta and innominate artery. This case is of further interest in that Osler (Osler and McCrae, 1908) personally examined Hare's patient on several occasions and stated : " It was not a case of throbbing of the innominate and the right carotid during ventricular systole, but there was a prominent dilated tumour to be grasped between the fingers just above the sternal notch. . . . At the post-mortem it was not a surprise to find the condition had been one of simple dynamic dilatation."

We have notes of four cases of aortic incompetence in which, besides the

usual carotid throbbing, there was a localized pulsatile swelling at the root of the neck on the right side. The swelling was rather more mesial than was that described as a typical kinked carotid, lying partly in the suprasternal notch and partly behind the right sternomastoid. Here the swelling appeared to be formed by the innominate artery, the origin of which was displaced to the left, so that the vessel crossed the episternal notch from left to right, in front of the trachea. Of our four cases, three were women aged 59, 60, and 67, and one was a man aged 55. All had hypertension and in three the Wassermann reaction was positive.

Group III. With Coarctation of the Aorta (3 *cases*)

In this congenital anomaly the subclavian arteries are often enlarged and pulsate excessively, but the carotids are not usually affected. We have, however, seen three cases of coarctation with abnormal pulsation in the suprasternal notch or at the root of the neck, not unlike that described under kinked carotid. Two were males, aged 14 and 25, and one was a female, aged 54. The swelling is probably due to elevation and dilatation of the aortic arch and a resultant high bifurcation of the innominate, though another possible explanation is an anomalous origin or course of the vessels springing from the aortic arch. Weber and Price (1912) described a female patient, aged 56, with aortic coarctation, in whom there was " a pulsating aneurysmal swelling on the right side of the neck, in front, just above the clavicle, about the average size of a hen's egg." If coarctation is suspected, confirmatory signs such as the diminutive femoral pulse and the collateral vessels should be sought, and X-rays may reveal an abnormal configuration of the aorta and the characteristic erosive notches on the lower borders of the ribs (Roesler's sign). When a vascular swelling of the root of the neck is found in a male or any young subject with hypertension, in whom the common form of carotid kinking is almost unknown, coarctation is the most likely explanation for it.

Group IV. With Other Congenital Vascular Anomalies

Tortuosity of the internal carotid artery has long been recognized by laryngologists as a developmental abnormality, occurring in the young and often bilaterally. The internal carotid artery originates from the third aortic arch and the dorsal aorta, and at the junction of the two component parts a distinct bend is formed. Kelly (1924) attributed the persistence of undulation or tortuosity to the fact that the normal straightening out of the artery is incomplete. It is manifested by a symptomless pulsating bulge in the lateral part of the pharynx. Kelly reviewed a series of 150 cases which included 21 over the age of 60 (these were believed to be arteriosclerotic) and found that females preponderated. Where the condition was unilateral, it was commoner on the right side.

Freyberger (1898) reported a female patient, aged 26, in whom " a pulsating swelling was visible above the right sterno-clavicular articulation ; its centre was covered by the sternal and clavicular insertions of the sterno-mastoid

muscle (the swelling measured 1½ inches from side to side, and about 1 inch from above downwards)." The clinical diagnosis was aneurysm of the innominate artery. At necropsy, the findings were a bulging body caused by an abnormally wide truncus brachiocephalicus into which were inserted the thyroidea ima and left common carotid artery. This short common trunk was in front of the trachea and measured half an inch across. It gave off the right subclavian, right common carotid, thyroidea ima, and left common carotid arteries. The left subclavian artery was in its normal place and position.

Anatomy, Pathology, and Causation

Anatomy

The innominate artery is the first and largest branch of the aortic arch, arising at the level of the upper border of the second right costal cartilage and passing upwards and slightly outwards to bifurcate behind the right sterno-clavicular joint. According to measurements cited by Krause (1868) its usual length is 2·5–5 cm., but in 16 of 219 cases from Quain it exceeded 5 cm. and might even exceed 7 cm. Burns (1809) observed instances of the innominate ascending in front of the trachea well above the top of the sternum before dividing, and mentions a cast in his possession showing the right carotid crossing the trachea two and a quarter inches above the sternum. The right common carotid artery arising from the innominate passes directly upwards in the neck as far as the thyroid cartilage, where it divides to form the external and internal carotid arteries ; no branches are given off. Its course is indicated by a line drawn from a point midway between the angle of the jaw and the mastoid process to the sterno-clavicular articulation.

Pathology

Necropsies were obtained in two of our cases summarized below, and in addition we have notes of a third necropsy in which a sketch of the tortuous innominate artery was made.

(1) *Case* 37.—An obese woman, aged 41, admitted with shortness of breath, failing vision, and vomiting. A pulsating vascular swelling occupied the right half of the suprasternal notch and extended to the right beneath the right sterno-mastoid muscle. B.P., 235/140 ; gallop rhythm ; extensive albuminuric retinitis ; W.R., negative ; blood urea, 455 mg. per 100 c.c. Death two weeks later.

Summary of necropsy. Renal insufficiency. Nephritis repens. Considerable cardiovascular hypertrophy. The carotids upon exposure showed no curvature. The innominate artery measured 1·05 cm. in diameter ; the right common carotid, 2 cm. from its origin, 0·65 cm. ; and the left 0·6 cm. The subclavian artery was slightly widened just beyond its origin (Fig. 5), but unfortunately its diameter was not recorded and no portion was taken for microscopic section. The heart was removed with the neck organs for the illustration and was not returned for weighing.

Longitudinal sections were taken from the proximal and distal parts of each common carotid artery and from the innominate artery, aortic arch, and abdominal aorta. Paraffin sections were stained with hæmatoxylin and eosin, Weigert's iron hæmatoxylin, and Ponceau S, Weigert's fuchsin, and neutral red for elastic fibres, and thionin according to Hoyer's method for mucin.

In the media of the *proximal portions of the right and left common carotid arteries* the elastic content was normal, the collagenous stroma was slightly increased, and there was mucous degeneration, which for the most part was confined to a zone beneath the intima but in one segment of each artery extended almost to the ad-

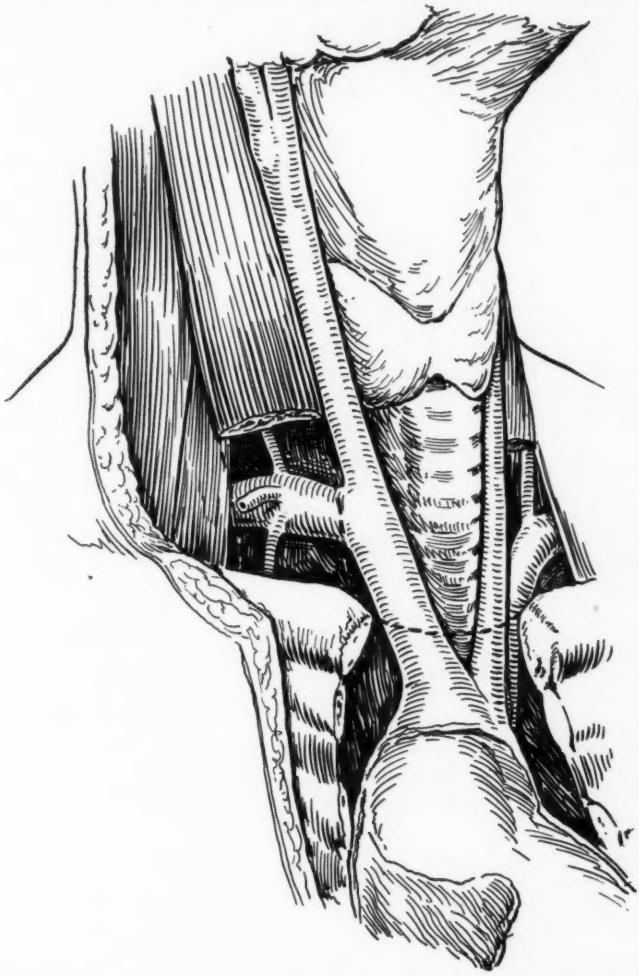

FIG. 5.—Drawing of aorta and great vessels in situ, post mortem, showing high bifurcation of innominate and slight localized dilatation of right subclavian (Case 37). Level of upper border of sternum indicated by dotted line.

ventitia. The degeneration was very slight upon the right side and moderate upon the left. On the other hand intimal hypertrophy was greater on the right side (1/15 to 2/3 of the depth of the media as opposed to 1/13 to 1/4 on the left) and showed slightly more degeneration, three small areas of fatty atheroma being present. In the *distal portions* mucous degeneration was greater on the right side and involved

more of the media; it was not, however, severe. Intimal hypertrophy was much greater upon the right side, being from 3/4 to 9/10 of the depth of the media as opposed to 1/9 to 1/3 on the left. Further, the intima on the right side showed considerable mucous degeneration, while that on the left was free. In the *innominate artery* mucous degeneration of the media was very slight and patchy. In its depth and the amount of degeneration the intima was very similar to that of the proximal part of the left common carotid artery. In the *aorta*, particularly the abdominal portion, medial degeneration was greater than in the above arteries. In the *arch* the elastic was intact but there was a focal fusiform area in the centre of the coat in which muscle fibres were absent. There was considerable mucous degeneration, chiefly in the inner third. The depth of the intima was from 1/10 to 2/7 that of the media. In the *abdominal segment* the media was in general narrow, and it was very narrow at one spot where there were small areas in which the elastic fibres were fragmented or absent. There was a little mucus in the inner layers. The depth of the intima was two and a half times that of the very narrow segment of the media and half that of the media elsewhere. It showed much mucous degeneration in its outer part and a considerable number of foam cells.

The degeneration in the arteries was not greater than might be expected in view of the age of the patient and the persistent high blood pressure, which was known to have been present and very high for a year and a half and was doubtless of much longer duration. The degeneration of the media of the proximal portion of the right common carotid artery was not sufficient to have caused an aneurysmal dilatation appreciable clinically. It was, indeed, less than in the corresponding portion of the left artery.

(2) *Case* 40.—Well-nourished woman, aged 43, admitted with a view to operation for " innominate aneurysm." Pulsating swelling in the suprasternal notch and under the right sterno-mastoid muscle in the adjoining supraclavicular region. B.P., 210/140; W.R., negative; blood urea, 285 mg. per 100 c.c. X-ray, great cardiac enlargement and pulmonary congestion. Death a fortnight later.

Pathological summary. Hypertensive failure. Uræmia. Myocardial hypertrophy. Severe uræmic changes in kidneys. Terminal suppurative bronchiolitis. Œdema of lungs. Innominate artery branched at about two inches above the right sterno-clavicular joint; no kinking or dilatation noted.

(3) *Case X*.—Male, aged 74, admitted with the clinical diagnosis of hypertension and congestive heart failure.

Necropsy. Heart weighed 14 oz. (397 g.). The aortic arch was dilated and its summit reached the level of the upper borders of the clavicles. The innominate artery was tortuous and dilated, forming a loop which arched across the suprasternal notch from left to right (Fig. 6). The left carotid and subclavian arteries were also tortuous. There was severe kyphosis.

Five published cases with necropsies have already been cited. In Coulson's case the aorta was dilated and elongated and the right common carotid " reduplicated "; in Douglas Powell's case there was atheroma, a high division of the innominate, and a tortuous or bent right common carotid; in Balfour's case there was scoliosis and angulation of the aorta with displacement to the left of the dilated innominate artery, which was two inches long. In Hare's case with aortic incompetence, in which there was an egg-shaped tumour in the suprasternal notch, Osler stated that the condition was one of dynamic dilatation. Finally, in Freyberger's case the vascular swelling proved at necropsy to be a wide and anomalous innominate trunk.

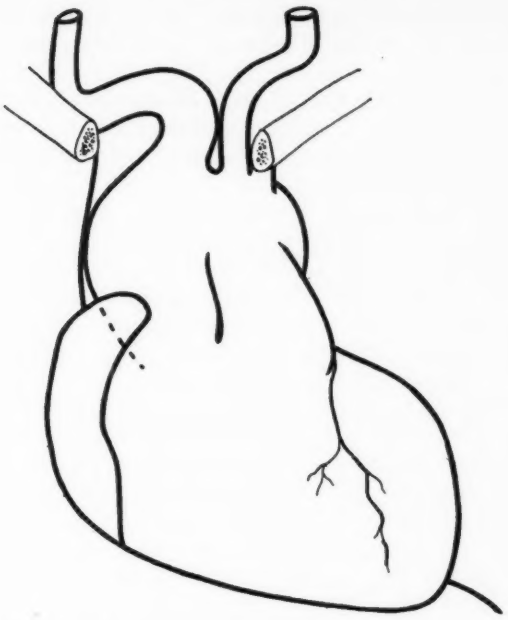

FIG. 6.—Outline drawing of the heart and great vessels in situ from a case of hypertension with kyphosis, showing high, tortuous and somewhat dilated inominate artery.

Causation

Available post-mortem observations show, therefore, that the vascular swelling in question is not due to aneurysm or localized dilatation of an artery, but to a tortuosity either of the right common carotid or of the innominate or of both, together with some degree of general dilatation of these arteries. Elongation and unfolding of the aorta with consequent displacement and elevation of the innominate is usually found. A high bifurcation of the innominate is due either to an unusual length of this artery or to elevation of its origin at the aorta or to both.

The frequency of hypertension is significant. Not only does hypertension produce uncoiling or unfolding of the aortic arch, often with some degree of dilatation, but it also accentuates the dynamic factor. When arteriosclerosis of the aorta is also present, as is usual, there is actual lengthening of the aorta. Thus the aortic arch becomes elevated in relation to the clavicles, and this elevation will be accentuated if the chest is shortened by kyphosis and by the high diaphragm of obesity.

The dynamic factor in these vascular swellings is clearly important, for the bulge seen in life usually disappears after death when the artery is no longer distended under high pressure. A tortuous or looped right carotid or innominate artery will receive direct the full force of a hypertrophied left ventricle, and at each systole an exaggerated movement is imparted to the arterial loop

comparable with that seen in a tortuous brachial artery when the forearm is bent. If aortic incompetence is added to hypertension, this dynamic factor will be reinforced.

As this abnormal pulsation occurs almost exclusively on the right side, an explanation should first be sought in the anatomical differences between the two sides. On the left side the carotid artery is free and has a long course between its origin and the skull, so that any tortuosity might be evenly distributed over its whole length. On the right side, however, the innominate artery and its direct continuation upwards as the carotid artery is anchored quite near the aorta by the right subclavian artery, and therefore elevation of the origin of the innominate will tend to cause a relatively acute kink at the site of the origin of the subclavian. The latter vessel passes backwards and to the right, between the scalene muscles, and any redundant length between the innominate and the fixed part of the subclavian will tend to force the bifurcation of the innominate forwards with each systole. The carotid in addition is relatively fixed at its termination, so that the tortuosity and kinking which form the aneurysm-like swelling lie at the bifurcation of the innominate, particularly at the commencement of the carotid artery, and may involve the adjacent part of the subclavian artery in addition.

The possibility of a congenital factor must be considered in view of the somewhat similar tortuosity of the internal carotid, which has been explained on an embryological basis. In this connection it is interesting to find two pairs of sisters in our forty cases.

To sum up, the vascular swelling consists of an arterial bend or loop in the region of the bifurcation of the innominate artery. It may be composite, and the degree which the carotid itself, the innominate, or even the subclavian artery may contribute to the pulsation is often hard to determine. Even necropsy may fail to reveal its exact nature where the dynamic factor has been predominant in its production.

Differential Diagnosis

(1) *Carotid Aneurysm*

In a tabulation of 551 published cases of aneurysm involving various arteries by Crisp (1847) the proportion of females to males was less than one to eight ; while in the 25 cases of carotid aneurysm there were 13 males to 12 females. Matas (1909) compared the occurrence of aneurysm in the carotid with that in other arteries, and stated that one third of the aneurysms in women occur in the carotid vessels. It is remarked also by Rose and Carless (1937), in reference to carotid aneurysm, that no other external vessel is so frequently the seat of aneurysm in women. Matas also said that the right carotid is more frequently the seat of aneurysm than the left ; the points of election are at the origin on the right side, where the carotid is given off from the innominate, and slightly less commonly at its bifurcation. In addition, " carotid aneurysms are usually of small size ; they are more often ovoid in form, their long axis lying parallel to that of the vessel."

In a careful search of the clinical records of the London Hospital during the period 1918–38, not a single case of aneurysm of the proximal portion of the right carotid artery was found. There are two specimens of carotid aneurysm in the museum of the Royal College of Surgeons ; one is in the left artery adjoining the aorta, which is also affected by aneurysmal dilatation, and the other is situated at the distal (upper) end of the right carotid where it bifurcates.

A detailed account of 142 cases of aneurysm treated surgically at the Johns Hopkins Hospital has been given by Reid (1926). Included in this number are ten cases (three female) of aneurysm of the common carotid artery, four being situated at the terminal bifurcation of the left vessel. Of the six cases of aneurysm involving the right common carotid artery, three of them lay at the distal (upper) end, whilst of the remaining three, one was continuous with an aneurysm of the innominate artery and the other two were undoubted examples of kinked carotid. One was a female, aged 54, with a history of throbbing in the neck and a systolic blood pressure of 200 mm. At operation no aneurysm was found, the vessel being simply arteriosclerotic. The other case was also a female, aged 46, with no symptoms, but presenting a pulsating swelling in the right side of the neck. The systolic blood pressure was 220 mm., the Wassermann reaction negative, and her arteries were thickened. At operation, no aneurysm was found and it was considered " a case of tortuous sclerotic vessel forced into an S shape."

We are unable to discover a single proven case of isolated aneurysm of the right carotid artery near its origin. The condition must be one of great rarity ; when aneurysm does occur, it is only an extension of an innominate aneurysm —the basic lesion. If, then, aneurysm of the right common carotid is so great a rarity, its frequency as reported in text books and in statistics based on clinical data is fallacious and arises from confusion between aneurysm at this site and kinked carotid. Aneurysm of the right common carotid artery near its origin should therefore not be diagnosed as a separate entity. A pulsating tumour in the right side of the neck in a patient over the age of 40, in the absence of congenital anomalies already discussed, should be considered a kinked carotid, unless it is accompanied by signs and symptoms of pressure on adjacent structures and by radiological or other evidence of involvement of the innominate and aorta.

(2) *Innominate Aneurysm*

Aneurysm of the innominate artery may be present as a small palpable swelling with visible pulsation in the supraclavicular fossa, a fullness above the sternal end of the right clavicle, or a pulsating tumour just above and to the right of the sterno-clavicular joint, spreading characteristically upwards under the sterno-mastoid muscle (Eschenbach, 1923 ; Norris and Landis, 1938 ; Rose and Carless, 1937 ; Parks, 1938).

There are many points of difference from kinked carotid. Innominate aneurysm is three times more common in men than in women (Eschenbach,

1923). Throbbing in the neck is usually associated with pain and dyspnœa and local pressure symptoms—arterial, venous, nervous, tracheal, or œsophageal. The lower border of the swelling cannot be defined, for it extends behind the clavicle. The Wassermann reaction is usually positive and syphilitic involvement of the adjoining aorta is invariable (Warfield, 1935). X-ray examination is usually conclusive, showing a tumour of the superior mediastinum rising on the right side at the upper level of the arch of a dilated aorta (syphilitic) and extending above the inner end of the clavicle. In oblique views, a fusiform shadow originating at the arch of the aorta bulges posteriorly and so causes compression of the trachea—a constant feature (Warfield, 1935). The aortic knuckle is sometimes depressed, whereas in kinked carotid it is high.

The differential diagnosis, therefore, rests on the absence on palpation of a lower limit to the swelling in the neck, a positive Wassermann reaction, the association of pressure symptoms and signs, and the X-ray appearance of the aorta and mediastinum.

(3) *Exaggerated Carotid Pulsation*

Prominent pulsation of the carotid arteries is bilateral in such conditions as neurosis, extreme anæmia, aortic incompetence, and thyrotoxicosis. In hypertension it is frequently right-sided, and of 105 cases of hypertension investigated by Bolotin (1933) 30 per cent. showed pulsation on the right, whereas 24 per cent. had bilateral carotid pulsation, and only 6 per cent. left-sided pulsation alone. This tendency for carotid pulsation to be greater on the right side in hypertension is due in part to those factors that sometimes produce an actual swelling, i.e. kinked carotid.

(4) *Other Conditions: Venous Pulsation*

A dilated jugular bulb occasionally appears as a pulsating sac above the clavicle, especially in tricuspid incompetence. There is also a varix of the right external jugular vein (Hunter, 1927). Goitre affecting the right lobe, especially if cystic, may resemble the condition superficially, as may a cervical rib displacing vessels in the neck. Tumours or enlarged and adherent cervical glands with transmitted impulse may enter into differential diagnosis. Banks-Davis (1924) and Ballance (1924) have both related errors in the diagnosis of a pulsating abscess, especially where an eroded artery has ruptured and given rise to a pulsating hæmatoma or an infected suppurating aneurysm.

Summary

An aneurysm-like swelling on the right side of the neck, the so-called kinked carotid, is described on the basis of 47 cases and a review of the cases published previously.

The common form of kinked carotid is generally associated with hypertension—often with hypertension combined with arteriosclerosis—but sometimes with arteriosclerosis alone (25 per cent.). It occurs in middle-aged and older women, especially in those affected by spinal curvature and obesity, and it is

scarcely ever seen in men. The swelling itself produces no symptoms beyond local throbbing; it changes little if at all in the course of years, and it has no bearing on prognosis. X-ray examination shows elevation of the aortic arch due to lengthening and uncoiling of the aorta, aided by a high diaphragm. Attention is drawn to an abnormal shadow sometimes cast by the kinked carotid, which partly obscures the apex of the right lung.

A comparable vascular swelling may be associated with aortic incompetence, coarctation of the aorta, and other congenital vascular anomalies.

The swelling consists of an arterial prominence with tortuosity in the region of the innominate bifurcation, which is often elevated. It may be formed by a loop of the right carotid, though the innominate itself or even the subclavian may contribute. Atheroma of the aorta and these branches is usually present, but not syphilis. The dynamic factor, accentuated by hypertension, is important in the production of the swelling. The necropsy findings in three cases are reported.

Differential diagnosis is discussed chiefly in reference to aneurysm of the right common carotid artery, for which it is frequently mistaken. The occurrence of isolated aneurysm of the proximal portion of the carotid artery, unless traumatic, is doubted; surgical operations performed for such an aneurysm most often discover no more than a kinked carotid.

We wish to thank especially Dr. Donald Hunter for much help with our early observations and for obtaining the post-mortem drawing in Fig. 5. Dr. R. A. Rowlands, Professor Ellis, Dr. William Evans, Dr. Paul Wood, Dr. Doris Baker and Mr. Pearce Gould kindly gave us permission to investigate and record cases under their care; and Sir James Walton kindly advised us on the surgical aspect. We are indebted to Professor Turnbull for the pathological report on Case 37 and to Professor McIntosh for that on Case 40. The Editor of the *Middlesex Hospital Journal* has permitted the reproduction of Fig. 1.

Illustrative Cases

Group I. With Hypertension or Arteriosclerosis.

Case 1.—Female, aged 52. Sought advice for a lump on the right side of the neck, thought to be gradually increasing in size and noticed for two years.

Examination (1923). A thin and bent patient with a prominent pulsating swelling, the size of a walnut, rounded, beneath right sterno-mastoid muscle, near the sternum, in the position of the right carotid artery. Aneurysm suspected and operation considered.

Course.—In 1927, swelling as in 1923 or larger. Slight left carotid pulsation without any swelling. B.P., 175/75. W.R., negative. X-ray: left ventricle moderately enlarged, aorta unfolded and summit reaches clavicle. Blood pressure: 1928, 140/70; 1929, 135/80; 1930, 155/85. In 1935 death, with hemiplegia.

Case 2.—Female, aged 79. A swelling on the right side of the neck was noted first at hospital in 1913 and again in 1920.

Examination (1938).—Average weight, not stout. Visible pulsation of the right carotid artery at the level of the thyroid cartilage; a little lower down there was a pulsating swelling the size of a pigeon's egg. It extended from the left of the middle of the episternal notch to behind the right sterno-mastoid muscle and then slightly external to it. Its course was upwards and to the right; there was a forward and then a lateral kink before it turned somewhat posteriorly and then upwards to the normal position of the common carotid artery. The swelling was more noticeable on lying

down. Slight general kyphosis ; moderate scoliosis to the right. B.P., 260/105. Radial and brachial arteries consistent with age ; no abnormal tortuosity. W.R., negative. X-ray : left ventricle enlarged ; aorta unfolded and elongated, the summit reaching the lower border of the clavicle. A pulsating, faint shadow continuous with the denser aortic shadow extended upwards from below the right clavicle to the apex of the right lung, which it obscured (Fig. 3). When the patient was turned slightly to the right, it filled the centre of the clear space of the right apex. Palpation confirmed that this was due to the pulsating swelling noted in the neck. The diaphragm was not raised.

Case 3.—Female, aged 64. Referred by her own doctor on account of " pulsating swelling in the right side of the neck ; I think, an aneurysm."

Examination (1936).—Expansile swelling, round, size of a walnut, above the right sterno-clavicular joint, in the position of the proximal part of the right common carotid artery. It was visible and palpable both internal and external to the sterno-mastoid muscle, equally prominent lying or standing. High dorsal scoliosis to the right, and considerable kyphosis. B.P., 165/80. Brachial and radial arteries were not unduly thickened nor tortuous. X-ray : left ventricle enlarged ; aorta elongated, the summit reaching the upper border of the left clavicle.

Course.—In 1938, no increase in size of swelling. B.P., 195/100. X-ray : left ventricle enlarged ; elongation of aorta, with summit reaching above the left clavicle.

Case 4.—Female, aged 65. Swelling in the right side of the neck, of five years' duration.

Examination (1932).—Round pulsating swelling above the inner end of the right clavicle, extending from the middle of the suprasternal notch to a point external to the right sterno-mastoid muscle and projecting this muscle. B.P., 280/140. X-ray : left ventricle considerably enlarged ; wide vascular pedicle with elongation of the aorta so that the summit of the aortic knuckle appeared well above the upper border of the left clavicle, obscuring the inner portion of the apex of the left lung. The apex of the right lung was also obscured in its inner half by a shadow with an outward convexity which was shown during radioscopy to be subjacent to the pulsatile vascular swelling in the neck (Fig. 4). The diaphragm was high.

Course.—She died suddenly at home the same year (1932).

Group II. With Aortic Incompetence.

Case 5.—Female, aged 59. History of swelling of the right side of the neck.

Examination (1938).—Pulsating swelling, as large as a hen's egg, above the inner end of the right clavicle ; it projected medially, and its upper and outer portion curved laterally and then medially to attain the normal position of the right common carotid artery. Aortic diastolic murmur ; pulse collapsing ; radial and brachial arteries thickened and moderately tortuous. B.P., 220/60. W.R., positive. X-ray : heart enlarged to the left, aorta elevated and slightly widened.

Group III. With Coarctation of Aorta.

Case 6.—Male, aged 25. Pulsating swelling noticed in the neck for many years.

Examination (1927).—Pulsating swelling in the right side of the neck, situated in the suprasternal notch and also under the right sterno-mastoid muscle. The bifurcation of the innominate artery was palpable above the clavicle, and the right common carotid seemed dilated and tortuous. The pulsating swelling appeared to be caused by the tortuosity of the common carotid. The temporal and external carotid arteries were dilated and tortuous, and pulsated excessively. Loud systolic murmur at the base ; aortic second sound loud and ringing, followed by a short soft aortic diastolic murmur. B.P., 195/85, right arm. Femoral pulse almost absent. X-ray : considerable enlargement of left ventricle ; aortic arch high, ascending aorta much dilated and the pulsation exaggerated.

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